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Relapse and Disease-Free Survival in Patients With Myelodysplastic Syndrome Undergoing Allogeneic Hematopoietic Cell Transplantation Using Older Matched Sibling Donors vs Younger Matched Unrelated Donors

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IMPORTANCE Matched sibling donors (MSDs) are preferred for allogeneic hematopoietic cell transplantation (allo-HCT) in myelodysplastic syndrome even if they are older. However, whether older MSDs or younger human leukocyte antigen–matched unrelated donors (MUDs) are associated with better outcomes remains unclear.

OBJECTIVE To investigate whether allo-HCT for myelodysplastic syndrome using younger MUDs would be associated with improved disease-free survival and less relapse compared with older MSDs.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study assessed data reported to the Center for International Blood and Marrow Transplant Research database from 1761 adults 50 years or older with myelodysplastic syndrome who underwent allo-HCT using an older MSD or younger MUD between January 1, 2011, and December 31, 2017, with a median follow-up of 48 months. Data analysis was performed from January 8, 2019, to December 30, 2020.

INTERVENTIONS/EXPOSURES Allo-HCT from an older MSD (donor age ≥50 years) or a younger MUD (donor age ≤35 years).

MAIN OUTCOMES AND MEASURES The primary outcome was disease-free survival. Secondary outcomes were overall survival, relapse, nonrelapse mortality, acute graft-vs-host disease (GVHD), chronic GVHD, and GVHD-free relapse-free survival.

RESULTS Of 1761 patients (1162 [66%] male; median [range] age, 64.9 [50.2-77.6] years in the MSD cohort and 66.5 [50.4-80.9] years in MUD cohort), 646 underwent allo-HCT with an older MSD and 1115 with a younger MUD. In multivariable analysis, the rate of disease-free survival was significantly lower in allo-HCTs with older MSDs compared with younger MUDs (hazard ratio [HR], 1.17; 95% CI, 1.02-1.34; $P = .02$), whereas the difference in overall survival rate of allo-HCT with younger MUDs vs older MSDs was not statistically significant (HR, 1.13; 95% CI, 0.98-1.29; $P = .07$). Allo-HCT with older MSDs was associated with significantly higher relapse (HR, 1.62; 95% CI, 1.32-1.97; $P < .001$), lower nonrelapse mortality (HR, 0.76; 95% CI, 0.59-0.96; $P = .02$), lower acute GVHD (HR, 0.52; 95% CI, 0.42-0.65; $P < .001$), chronic GVHD (HR, 0.77; 95% CI, 0.64-0.92; $P = .005$), and a lower rate of GVHD-free relapse-free survival beyond 12 months after allo-HCT (HR, 1.42; 95% CI, 1.02-1.98; $P = .04$).

CONCLUSIONS AND RELEVANCE This cohort study found higher disease-free survival and lower relapse for allo-HCT in myelodysplastic syndrome using younger MUDs compared with older MSDs. The risk of nonrelapse mortality and GVHD was lower with older MSDs. These results suggest that the use of younger MUDs should be considered in the donor selection algorithm for myelodysplastic syndrome, in which it is pivotal to minimize relapse given limited treatment options for managing relapsed disease.

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Supplemental content

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Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative treatment for myelodysplastic syndrome. With the advent of reduced-intensity conditioning and more donor options, the use of allo-HCT has increased over time.[1] However, the benefits need to be weighed against the risk of complications because these patients are often older adults.[2] Disease relapse remains a major issue after allo-HCT and portends a poor prognosis.[3] Efforts to minimize relapse and understand the causes of treatment failure are important in improving the long-term prognosis. Although several factors influence the outcomes of allo-HCT, donor age and donor-recipient human leukocyte antigen (HLA) match are of crucial importance.[4-10] A large study[10] from the Center for International Blood and Marrow Transplant Research of more than 10 000 patients found that donor-recipient HLA mismatch and older donor age were associated with poor outcomes. Similarly, another study[11] that evaluated the association of donor-recipient HLA match with outcomes in hematological malignant cancers found that HLA-matched sibling donors (MSDs) are associated with improved outcomes. Hence, in clinical practice, MSDs are considered the preferred choice.

Still, one must take into consideration that myelodysplastic syndrome is a disease of older adults and sibling donors are also likely to be older with issues such as comorbidities, risk of clonal hematopoiesis of indeterminate potential, and impaired immune and regenerative potential of stem cells.[12-15] Although younger HLA-matched unrelated donors (MUDs) are an important alternative in this context, it remains unclear whether the use of MUDs is associated with better outcomes. Prior single-center and registry studies[10,16,17] that addressed this question yielded conflicting results and were not focused exclusively on myelodysplastic syndrome. Hence, we sought to determine the association of donor age and type with the outcomes of allo-HCT for myelodysplastic syndrome by comparing 2 common donor groups: older MSDs and younger MUDs. We hypothesized that allo-HCT using younger MUDs compared with older MSDs would be associated with improved disease-free survival and lower relapse.

Key Points

Question In adults with myelodysplastic syndrome, could allogeneic hematopoietic cell transplantation (allo-HCT) using younger matched unrelated donors help reduce relapse and improve disease-free survival compared with older matched sibling donors?

Findings In this cohort study of 1761 patients with myelodysplastic syndrome, allo-HCT using younger matched unrelated donors was associated with significantly lower relapse rates and higher disease-free survival compared with allo-HCT using older matched sibling donors.

Meaning These results suggest that the use of younger matched unrelated donors could be a potential way to help prevent relapse after allo-HCT in myelodysplastic syndrome given limited treatment options and poor prognosis for relapsed disease.

Methods

Study Objectives and Data Source

This cohort study compares the disease-free survival, overall survival, relapse, nonrelapse mortality, acute graft-vs-host disease (GVHD), chronic GVHD, and GVHD-free relapse-free survival in 1761 patients with myelodysplastic syndrome undergoing allo-HCT from older MSDs or younger MUDs. The Center for International Blood and Marrow Transplant Research is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program that comprises a voluntary network of more than 450 transplantation centers that contribute baseline and posttransplantation data on consecutive hematopoietic cell transplantations to a centralized statistical center.[18] Observational studies with this database are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. All participants provided written informed consent. Protected health information used in the performance of such research is collected and maintained in the researchers' capacity as a public health authority under the Health Insurance Portability and Accountability Act Privacy Rule. The institutional review boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Patients and Outcomes

Adults 50 years and older with myelodysplastic syndrome who underwent first allo-HCT with an older MSD (donor age ≥50 years) or a younger 8/8 HLA-matched (HLA-A, -B, -C, and -DRB1) MUD (donor age ≤35 years) were included. Patients with primary and secondary myelodysplastic syndrome (including therapy related) were eligible. The study was performed from January 1, 2011, to December 31, 2017, to include a recent cohort of patients from the data set. Data analysis was performed from January 8, 2019, to December 30, 2020. Because prior studies[10,16,19-21] using unrelated donors reported a survival advantage with younger MUDs between the ages of 30 and 36 years, we restricted the MUD arm to a donor age of 35 years or younger because including older MUDs would not support our study hypothesis. Given that sibling donors are likely to be around the same age as recipients, a donor age of 50 years or older was used for MSDs. Key exclusion criteria were allo-HCT from mismatched unrelated-donor, haploidentical-donor, syngeneic-donor, cord blood, and ex vivo T-cell depleted or CD34 selected grafts. To ensure homogeneity, patients receiving posttransplant cyclophosphamide for GVHD prophylaxis were excluded (eFigure 1 in the Supplement).

The primary outcome was disease-free survival. Secondary outcomes were overall survival, relapse, nonrelapse mortality, acute GVHD, chronic GVHD, and GVHD-free relapse-free survival (definitions provided in the eMethods in the Supplement).

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics with median (range) for continuous variables and numbers (percentages) for categorical variables. Cumulative incidence estimates were calculated for competing risks outcomes, including acute GVHD, chronic GVHD, nonrelapse mortality, and relapse. The Kaplan-Meier method was used to estimate survival probabilities. Multivariable Cox proportional hazards regression analysis for survival and the Fine-Gray model[22] for competing risks outcomes were used. The proportional hazards assumption was examined and covariates that violated the assumption were added as time-dependent covariates. In the absence of binary end points, hazard ratios (HRs) and 95% CIs were reported. Factors considered for multivariable analysis included patient age, donor age, sex match, cytomegalovirus match, ABO blood type match, disease subtype (primary, therapy related, or antecedent hematologic disorder), Revised International Prognostic Scoring System (IPSS-R) score at allo-HCT,[23] Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) score,[24] Karnofsky Performance Scale score, prior therapy, interval between diagnosis and transplant, conditioning intensity, stem cell source, GVHD prophylaxis, use of antithymocyte globulin and alemtuzumab, and year of transplant. A stepwise selection method was used to identify the final model with significance level of .05, and only factors that attained that significance are given (eTable 3 in the Supplement). Because of the potential for recipient age to influence outcomes, it was forced on all multivariable models. A pairwise comparison within the nonreference groups was also performed in multivariable models to demonstrate their association and shown as contrasts. Center effect was tested using the score test proposed by Commenges and Andersen,[25] and marginal Cox proportional hazards regression models were used for adjustments. Center effect was significant for all outcomes except overall survival and was adjusted accordingly. Missing category was included as 1 group to avoid loss of data and power.[26] All analyses were performed at a 2-sided significance level of $P < .05$ using SAS software, version 9.4 (SAS Institute Inc).

Results

Baseline Characteristics

Among 1761 eligible patients in this cohort study (1162 [66%] male; median [range] age, 64.9 [50.2-77.6] years in the MSD cohort and 66.5 [50.4-80.9] years in MUD cohort), 646 underwent allo-HCT with an older MSD and 1115 with a younger MUD. Baseline characteristics are summarized in eTable 1 in the Supplement. Most patients underwent allo-HCT with peripheral blood grafts, reduced-intensity conditioning, and tacrolimus-based GVHD prophylaxis. Notable differences in the MUD cohort included longer median interval from diagnosis to transplant (8.4 vs 7.3 months, $P = .02$), a higher percentage of bone marrow grafts (10.0% vs 2.0%, $P < .001$), a lower percentage of female donor–male recipient pairs (12.0% vs 31.0%, $P < .001$), a higher ABO blood type mismatch rate (48.0% vs 32.0%, $P < .001$), and higher antithymocyte globulin and alemtuzumab use (37.0% vs 14.0%, $P < .001$) compared with the MSD cohort. Median follow-up was 48.1 months (range, 3.2-99.5 months) in the MSD cohort and 46.0 months (range, 3.1-98.2 months) in the MUD cohort.

Survival

In univariate analysis (eTable 2 in the Supplement), 5-year disease-free survival was significantly higher in patients undergoing allo-HCT with younger MUDs (30.6%; 95% CI, 27.4%-33.8%) than with older MSDs (24.9%; 95% CI, 21.1%-28.9%; $P = .01$). In multivariable analysis, compared with allo-HCT with younger MUDs, disease-free survival was significantly lower in patients undergoing allo-HCT with older MSDs (HR, 1.17; 95% CI, 1.02-1.34; $P = .02$) (**Table** and **Figure 1**). Other factors significantly associated with disease-free survival were HCT-CI score, IPSS-R score, disease type, GVHD prophylaxis, and use of antithymocyte globulin and alemtuzumab (eTable 3 in the Supplement). The 5-year overall survival in univariate analysis was 37.1% (95% CI, 33.6%-40.6%) for patients undergoing allo-HCT with younger MUDs and 33.9% (95% CI, 29.6%-38.4%) for patients undergoing allo-HCT with older MSDs ($P = .19$). Overall survival was significantly associated with HCT-CI score, IPSS-R score, and antithymocyte globulin and alemtuzumab use but not donor type (older MSDs: HR, 1.13; 95% CI, 0.98-1.29; $P = .07$) (**Figure 2**; eTable 3 in the Supplement).

Relapse

Cumulative incidence of relapse at 5 years was significantly lower for patients undergoing allo-HCT with younger MUDs (37.3%; 95% CI, 34.3%-40.3%) than with older MSDs (49.6%; 95% CI, 45.5%-53.7%; $P < .001$) (eTable 2 in the Supplement). In multivariable analysis, the risk of relapse was significantly higher for allo-HCT with older MSDs (HR, 1.62; CI, 1.32-1.97; $P < .001$) compared with younger MUDs (Table and **Figure 3**). Other factors significantly associated with relapse included recipient age, use of antithymocyte globulin and alemtuzumab, IPSS-R score, and the interval between diagnosis to transplant (eTable 3 in the Supplement).

Nonrelapse Mortality

In univariate analysis, nonrelapse mortality at 5 years was 32.2% (95% CI, 29.0%-35.4%) for patients undergoing allo-HCT with younger MUDs and 25.5% (95% CI, 21.8%-29.4%) with older MSDs ($P = .002$) (eTable 2 in the Supplement). In multivariable analysis, a lower risk of nonrelapse mortality was seen for patients undergoing allo-HCT with older MSDs (HR, 0.76; 95% CI, 0.59-0.96; $P = .02$) (Table; eFigure 2 in the Supplement). Other factors significantly associated with nonrelapse mortality included HCT-CI score and Karnofsky performance score (eTable 3 in the Supplement).

Graft-vs-Host Disease

The 1-year incidence of acute GVHD grade II to IV was 39.3% (95% CI, 35.5%-43.1%) for patients undergoing allo-HCT with older MSDs and 48.3% (95% CI, 45.4%-51.3%) for patients undergoing allo-HCT with younger MUDs ($P = .001$) (eTable 2 in the Supplement). The 1-year incidence of grade III to IV acute

Table. Multivariable Analysis of Main Effect on Outcomes

Outcome	No. of patients	HR (95% CI)	*P* value
Disease-free survival (center effect)			
MUD cohort	1110	1.00 [Reference]	.02
MSD cohort	643	1.17 (1.02-1.34)	
Overall survival (no center effect)			
MUD cohort	1111	1.00 [Reference]	.07
MSD cohort	643	1.13 (0.98-1.29)	
Relapse (center effect)			
MUD cohort	1109	1.00 [Reference]	<.001
MSD cohort	643	1.62 (1.32-1.97)	
Nonrelapse mortality (center effect)			
MUD cohort	1110	1.00 [Reference]	.02
MSD cohort	643	0.76 (0.59-0.96)	
Acute GVHD grade II-IV (center effect)			
Main group (≤2 mo)			
MUD cohort	1102	1.00 [Reference]	<.001
MSD cohort	634	0.52 (0.42-0.65)	
Main group (>2 mo)			
MUD cohort	649	1.00 [Reference]	.25
MSD cohort	470	1.16 (0.90-1.51)	
Acute GVHD grade III-IV (center effect)			
Main group (≤2 mo)			
MUD cohort	1100	1.00 [Reference]	<.001
MSD cohort	633	0.55 (0.39-0.79)	
Main group (>2 mo)			
MUD cohort	888	1.00 [Reference]	.01
MSD cohort	552	1.66 (1.10-2.50)	
Chronic GVHD (center effect)			
MUD cohort	1104	1.00 [Reference]	.005
MSD cohort	638	0.77 (0.64-0.92)	
GVHD-free relapse-free survival (center effect)			
Main group (≤12 mo)			
MUD cohort	1090	1.00 [Reference]	.94
MSD cohort	632	1.00 (0.89-1.12)	
Main group (>12 mo)			
MUD cohort	211	1.00 [Reference]	.04
MSD cohort	107	1.42 (1.02-1.98)	

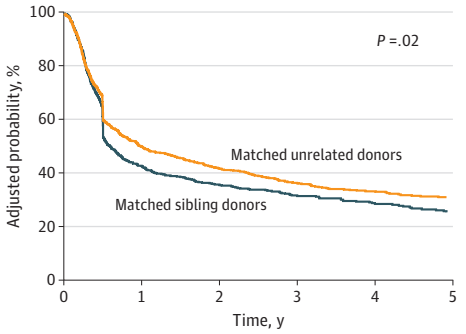
Abbreviations: GVHD, graft-vs-host disease; HR, hazard ratio; MSD, matched sibling donor; MUD, matched unrelated donor.

GVHD was 17.2% (95% CI, 14.4%-20.3%) for patients undergoing allo-HCT with older MSDs and 20.0% (95% CI, 17.7%-22.4%) for patients undergoing allo-HCT with younger MUDs ($P = .14$). The 5-year incidence of chronic GVHD was 49.0% (95% CI, 44.9%-53.0%) for patients undergoing allo-HCT with older MSDs and 53.9% (95% CI, 50.7%-57.1%) for patients undergoing allo-HCT with younger MUDs ($P = .08$). On multivariable analysis, older MSDs were associated with a lower risk of acute GVHD grades II to IV (HR, 0.52; 95% CI, 0.42-0.65; $P < .001$) and III to IV (HR, 0.55; 95% CI, 0.39-0.79; $P < .001$), and chronic GVHD (HR, 0.77; 95% CI, 0.64-0.92; overall $P = .005$) (Table; eFigures 3-5 in the Supplement). Other factors significantly associated with GVHD were conditioning intensity, GVHD prophylaxis, donor-recipient sex match, and HCT-CI score for acute GVHD and graft source, and antithymocyte globulin and alemtuzumab for chronic GVHD (eTable 3 in the Supplement).

GVHD-Free Relapse-Free Survival

Despite a small difference (6.3% vs 9.3% at 5 years in univariate analysis), older MSDs were associated with significantly lower GVHD-free relapse-free survival beyond 12 months of allo-HCT (HR, 1.42; 95% CI, 1.02-1.98; $P = .04$) but not within the first 12 months (analysis separated by these time points because of nonproportional hazard assumption). In addition, HCT-CI score, IPSS-R score, year of transplant, and graft type

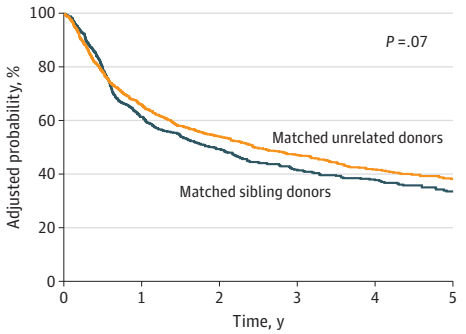
Figure 1. Disease-Free Survival by Donor Type



No. at risk

Matched unrelated donors	1110	528	363	253	161	96
Matched sibling donors	644	262	182	131	94	53

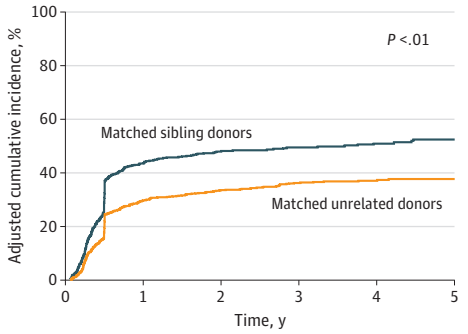
Figure 2. Overall Survival by Donor Type



No. at risk

Matched unrelated donors	1115	696	476	325	201	121
Matched sibling donors	646	384	261	181	127	70

Figure 3. Cumulative Incidence of Relapse



No. at risk

Matched unrelated donors	1110	535	366	254	162	98
Matched sibling donors	644	265	185	133	96	54

were also significantly associated with GVHD-free relapse-free survival (eFigure 6 and eTable 3 in the Supplement)

Discussion

Using the 2 most common donor groups for allo-HCT in myelodysplastic syndrome, this cohort study found higher disease-free survival, better GVHD-free relapse-free survival, and lower relapse rates for patients undergoing allo-HCT with younger MUDs compared with older MSDs. The difference in overall survival was not statistically significant, likely reflecting the effect of lower nonrelapse mortality and GVHD with MSDs. Several research efforts are currently focused on minimizing relapse after allo-HCT. Although many factors influence this outcome, donor age and HLA match status play vital roles.[27-29] If an older MSD and a younger MUD are available as donors, a common clinical question is whether one would be a better donor than the other. Although the conventional choice is MSDs, these donors are more likely to be older and to have age-related issues, including a decline in CD8 T lymphocytes and impaired T-cell–mediated graft-vs-tumor effect.[30] Younger MUDs are less likely to have these problems and could serve as a reasonable choice. We evaluated this question specifically in myelodysplastic syndrome, and our results enhance the clinical decision-making process.

Although prior studies[10,11,19,21] have evaluated the effect of donor age in different hematologic malignant cancers, myelodysplastic syndrome represented a smaller proportion (12%-13%) of the population studied. Some studies[16,17,31] have analyzed the impact of donor age specifically in MDS. A study by Saber et al[31] showed similar survival between MSD and MUD allo-HCT in myelodysplastic syndrome, although a comparison between younger MUDs vs older MSDs was not performed. A study[16] from the European Society for Blood and Marrow Transplantation showed higher overall survival with MUDs (age <30 years) compared with MSDs, although it included both patients with myelodysplastic syndrome and acute myeloid leukemia, introducing heterogeneity about the underlying disease. Our study provides a clear comparison between allo-HCT with younger MUDs vs older MSDs specifically in myelodysplastic syndrome. Other factors, such as conditioning intensity and donor-recipient sex match, mainly influenced the risk of GVHD. Disease subtype (primary vs therapy-related myelodysplastic syndrome) did not significantly influence overall survival.

To justify the rationale for preferring younger MUDs to minimize relapse, it is important to ensure that the time involved in waiting to find one does not compromise the outcomes. As expected, the time from diagnosis to allo-HCT was longer with MUDs, raising the possibility of those patients being stable to wait for allo-HCT. However, the difference in median time from diagnosis to allo-HCT between the 2 cohorts was only 1.1 months (7.3 vs 8.4 months) (eTable 1 in the Supplement). In addition, we checked for associations between time from diagnosis to allo-HCT and the main effect (older MSD vs younger MUD) in all multivariable models and did not find significant associations. Although the aspect of waiting for an appropriate donor vs immediately proceeding to allo-HCT with the earliest available donor is best analyzed through prospective clinical trials, our current models have carefully assessed this aspect and do not demonstrate any associations that would suggest bias toward the MUD cohort. Similarly, the possibility of disease risk (low vs high) affecting the timing of allo-HCT and the donor choice (older MSD vs younger MUD) was

assessed through associations between these factors in multivariable models, and no significant associations were found. Last, given the lack of effective therapies for managing relapsed and refractory myelodysplastic syndrome, preventing relapse and improving the disease-free survival is an important, clinically meaningful end point to be considered while choosing donors.

Limitations

The study has some limitations. Despite the large sample size, our study is limited because of a lack of information on HLA-DP status, genomic mutations, donor clonal hematopoiesis, and T-cell repertoire changes, which could explain the differences in outcomes. Given the retrospective design, we lacked information on pretransplant disease course, physicians' decisions, and time between donor search initiation and identification. Although we restricted the analyses to MSDs and 8/8 MUDs to minimize the effect of HLA mismatching, the latter group could have some mismatches if 9/10 or 10/10 HLA matching was available and influenced graft alloreactivity. Because of the nature of GVHD reporting in the data set, chronic GVHD was assessed as a whole outcome without further stratification (mild vs moderate vs severe). Some factors that attained statistical significance in multivariable analysis (eg, history of antecedent hematologic disorder) are limited by smaller sample size to draw meaningful inferences.

Conclusions

This cohort study suggests that allo-HCT with younger MUDs is associated with lower relapse rates, improved disease-free survival, and better GVHD-free relapse-free survival compared with allo-HCT with older MSDs in myelodysplastic syndrome. Given the higher risk of relapse with reduced-intensity conditioning commonly considered in older patients, choosing a younger MUD might potentially reduce relapse, provided the risk of GVHD and nonrelapse mortality is considered. Strategies to mitigate GVHD could reduce its morbidity and mortality and potentially improve overall survival. The results of this study add important information to the donor selection algorithms for these patients.

ARTICLE INFORMATION

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REFERENCES

1. D'Souza A, Fretham C, Lee SJ, et al. Current use of and trends in hematopoietic cell transplantation in the United States. *Biol Blood Marrow Transplant*. 2020;26(8):e177-e182. doi:10.1016/j.bbmt.2020.04.013

2. Ma X. Epidemiology of myelodysplastic syndromes. *Am J Med*. 2012;125(7)(suppl):S2-S5. doi:10.1016/j.amjmed.2012.04.014

3. Schmid C, de Wreede LC, van Biezen A, et al. Outcome after relapse of myelodysplastic syndrome and secondary acute myeloid leukemia following allogeneic stem cell transplantation: a retrospective registry analysis on 698 patients by the Chronic Malignancies Working Party of the European Society of Blood and Marrow Transplantation. *Haematologica*. 2018;103(2):237-245. doi:10.3324/haematol.2017.168716

4. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood*. 2007;110(13):4576-4583. doi:10.1182/blood-2007-06-097386

5. Nakasone H, Remberger M, Tian L, et al. Risks and benefits of sex-mismatched hematopoietic cell transplantation differ according to conditioning strategy. *Haematologica*. 2015;100(11):1477-1485. doi:10.3324/haematol.2015.125294

6. Ljungman P, Brand R, Hoek J, et al; Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Donor cytomegalovirus status influences the outcome of allogeneic stem cell transplant: a study by the European group for blood and marrow transplantation. *Clin Infect Dis*. 2014;59(4):473-481. doi:10.1093/cid/ciu364

7. Fleischhauer K, Shaw BE. HLA-DP in unrelated hematopoietic cell transplantation revisited: challenges and opportunities. *Blood*. 2017;130(9):1089-1096. doi:10.1182/blood-2017-03-742346

8. Bastida JM, Cabrero M, Lopez-Godino O, et al. Influence of donor age in allogeneic stem cell transplant outcome in acute myeloid leukemia and myelodisplastic syndrome. *Leuk Res*. 2015;39(8):828-834. doi:10.1016/j.leukres.2015.05.003

9. Seebach JD, Stussi G, Passweg JR, et al; GVHD Working Committee of Center for International Blood and Marrow Transplant Research. ABO blood group barrier in allogeneic bone marrow transplantation revisited. *Biol Blood Marrow Transplant*. 2005;11(12):1006-1013. doi:10.1016/j.bbmt.2005.07.015

10. Kollman C, Spellman SR, Zhang MJ, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. *Blood*. 2016;127(2):260-267. doi:10.1182/blood-2015-08-663823

11. Alousi AM, Le-Rademacher J, Saliba RM, et al. Who is the better donor for older hematopoietic transplant recipients: an older-aged sibling or a young, matched unrelated volunteer? *Blood*. 2013;121(13):2567-2573. doi:10.1182/blood-2012-08-453860

12. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med*. 2014;371(26):2488-2498. doi:10.1056/NEJMoa1408617

13. Miller RA. The aging immune system: primer and prospectus. *Science*. 1996;273(5271):70-74. doi:10.1126/science.273.5271.70

14. Chambers SM, Shaw CA, Gatza C, Fisk CJ, Donehower LA, Goodell MA. Aging hematopoietic stem cells decline in function and exhibit epigenetic dysregulation. *PLoS Biol*. 2007;5(8):e201. doi:10.1371/journal.pbio.0050201

15. Liang Y, Van Zant G, Szilvassy SJ. Effects of aging on the homing and engraftment of murine hematopoietic stem and progenitor cells. *Blood*. 2005;106(4):1479-1487. doi:10.1182/blood-2004-11-4282

16. Kröger N, Zabelina T, de Wreede L, et al; MDS subcommittee of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Allogeneic stem cell

transplantation for older advanced MDS patients: improved survival with young unrelated donor in comparison with HLA-identical siblings. *Leukemia*. 2013;27(3):604-609. doi:10.1038/leu.2012.210

17. Yam C, Crisalli L, Luger SM, et al. Unrelated donors are associated with improved relapse-free survival compared to related donors in patients with myelodysplastic syndrome undergoing reduced intensity allogeneic stem cell transplantation. *Am J Hematol*. 2016;91(9):883-887. doi:10.1002/ajh.24424

18. Horowitz M. The role of registries in facilitating clinical research in BMT: examples from the Center for International Blood and Marrow Transplant Research. *Bone Marrow Transplant*. 2008; 42(suppl 1):S1-S2. doi:10.1038/bmt.2008.101

19. Kollman C, Howe CW, Anasetti C, et al. Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. *Blood*. 2001;98(7): 2043-2051. doi:10.1182/blood.V98.7.2043

20. Carreras E, Jiménez M, Gómez-García V, et al. Donor age and degree of HLA matching have a major impact on the outcome of unrelated donor haematopoietic cell transplantation for chronic myeloid leukaemia. *Bone Marrow Transplant*. 2006; 37(1):33-40. doi:10.1038/sj.bmt.1705195

21. Shaw BE, Logan BR, Spellman SR, et al. Development of an unrelated donor selection score predictive of survival after HCT: donor age matters most. *Biol Blood Marrow Transplant*. 2018;24(5): 1049-1056. doi:10.1016/j.bbmt.2018.02.006

22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509. doi:10.1080/ 01621459.1999.10474144

23. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120(12): 2454-2465. doi:10.1182/blood-2012-03-420489

24. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106(8): 2912-2919. doi:10.1182/blood-2005-05-2004

25. Commenges D, Andersen PK. Score test of homogeneity for survival data. *Lifetime Data Anal*. 1995;1(2):145-156. doi:10.1007/BF00985764

26. Groenwold RHH, Dekkers OM. Missing data: the impact of what is not there. *Eur J Endocrinol*. 2020;183(4):E7-E9. doi:10.1530/EJE-20-0732

27. Scheid C, de Wreede L, van Biezen A, et al. Validation of the revised IPSS at transplant in patients with myelodysplastic syndrome/ transformed acute myelogenous leukemia receiving allogeneic stem cell transplantation: a retrospective analysis of the EBMT chronic malignancies working party. *Bone Marrow Transplant*. 2017;52(11):1519-1525. doi:10.1038/bmt.2017.171

28. Anasetti C, Logan BR, Lee SJ, et al; Blood and Marrow Transplant Clinical Trials Network. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367(16): 1487-1496. doi:10.1056/NEJMoa1203517

29. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35(11):1154-1161. doi:10.1200/ JCO.2016.70.7091

30. Reshef R, Huffman AP, Gao A, et al. High graft CD8 cell dose predicts improved survival and enables better donor selection in allogeneic stem-cell transplantation with reduced-intensity conditioning. *J Clin Oncol*. 2015;33(21):2392-2398. doi:10.1200/JCO.2014.60.1203

31. Saber W, Cutler CS, Nakamura R, et al. Impact of donor source on hematopoietic cell transplantation outcomes for patients with myelodysplastic syndromes (MDS). *Blood*. 2013;122(11):1974-1982. doi:10.1182/blood-2013-04-496778