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Relationship of donor age and relationship to outcomes of haploidentical transplantation with posttransplant cyclophosphamide

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Key Points

- The safety and effectiveness of mismatched transplants now allow consideration of donor selection by donor age and relationship.

Allogeneic blood or marrow transplantation (BMT) physicians seek to optimize all possible variables to improve outcomes. Selectable factors include conditioning, graft-versus-host disease (GVHD) prophylaxis, graft source, and donor. Many patients, especially those with eligible haploidentical (haplo) donors, will have multiple donor options. We seek to identify factors to optimize the choice of haplo donors when using posttransplantation cyclophosphamide (PTCy) GVHD prophylaxis. We evaluated the effect of modifiable donor characteristics (donor age and relationship) on outcomes following haplo BMT with a uniform nonmyeloablative conditioning and PTCy. From 2002 to 2017, 889 consecutive adult patients underwent nonmyeloablative haplo BMT with PTCy. Median follow-up among survivors was 2.5 years after BMT. Median recipient age was 59 (range: 18 to 76) years and median donor age was 40 (range: 13 to 79) years. Multivariable analyses demonstrated that increasing donor age by decade was associated with poorer overall survival (hazard ratio [HR], 1.13 [1.05, 1.22; $P = .0015$]), worse progression-free survival (HR, 1.09 [1.02, 1.16; $P = .015$]), and a higher risk for grade 2 to 4 and grade 3 to 4 GVHD (1.3 [1.06, 1.61; $P = .013$]), but not for chronic GVHD (HR, 1.06 [0.94, 1.2]; $P = .37$). These less-favorable results with older donors were attributable to worse nonrelapse mortality (HR, 1.19 [1.05, 1.34]; $P = .006$), not relapse. Parents were associated with inferior outcomes compared with sibling donors, whereas no significant differences were observed between parental donors. These data suggest that the youngest, adult-sized donors should be preferred when multiple haplo donors are available.

Introduction

Medical refinements over the years to allogeneic blood or marrow transplantation (alloBMT), including the advent of nonmyeloablative (NMA)/reduced intensity conditioning regimens and newer graft-versus-host disease (GVHD) prophylaxis regimens, now provide the vast majority of patients in need of the procedure a path to potential cure. Some centers now extend patient eligibility up to at least age 80.[1-3] With the development of newer GVHD regimens, such as posttransplantation cyclophosphamide (PTCy), essentially every patient now has a donor. In fact, most patients now have multiple donor options, with HLA-haploidentical (haplo) relatives (siblings, parents, children, second-/third-degree relatives) and even mismatched unrelated donors yielding similar outcomes to matched donors.[4-9] Accordingly, although donor characteristics are rarely modifiable in the matched sibling setting because of limited choices, the expanded pool of potential donors allows consideration of the impact of donor characteristics other than HLA matching on transplant outcomes.

In addition, studying particular donor characteristics in matched siblings has been problematic because of similarities between donors and recipients. For example, the similar age among siblings makes it

difficult to determine the effect of donor age independent from recipient age. However, the expanded use of matched unrelated donor BMT over the past 3 decades has allowed a variety of donor characteristics to be studied, often with variations in the findings, including sex,[10] ABO status,[11] cytomegalovirus (CMV) status, and donor age.[7,12-14] Other than degree of HLA match, donor age emerges as the most important donor characteristic affecting outcomes in large unrelated donor cohorts,[13] although, in general, patient characteristics and disease biology continue to supersede donor features for patient outcomes overall.[7,15,16] Some data even suggest that younger matched unrelated donors may result in better outcomes than older matched sibling donors.[17]

However, an assessment of outcomes based on donor age is potentially challenging in the haplo BMT setting, as it is confounded by donor-recipient relationship/kinship (Figure 1). For example, many patients may have both an older haplo sibling and a younger adult-sized haplo child as potential donors, whereas a younger patient may have an older haplo parent as well as a younger haplo sibling donor. Accordingly, understanding the impact of both donor relationship/kinship and age on transplant outcomes is critical to donor selection for haplo BMT. Although the impact of donor age/kinship on haplo BMT outcomes is beginning to be studied, results have been somewhat conflicting,[7,12] perhaps owing to the heterogeneity in the transplant platforms in these multicenter/registry analyses. Here, in a large cohort of patients at a single institution, we sought to determine the impact of donor age on transplant outcomes after haplo BMT utilizing uniform NMA conditioning and post-PTCy as GVHD prophylaxis.

Materials and methods

Patient and transplantation procedures

Institutional review board approval was obtained for this retrospective study of 889 consecutive patients undergoing BMT at Johns Hopkins Hospital from October 1, 2002 to December 31, 2017. All recipients of haplo-related donor T-cell replete blood or marrow grafts after NMA conditioning for a hematologic malignancy were included. Because of the small numbers of second- and third-degree related donors (6%), the analyses were initially performed with only recipients of first-degree related allografts and then repeated with the addition of second- and third-degree related donors. Conditioning was uniform and consisted of fludarabine, cyclophosphamide, and total body irradiation at 200 cGy as previously described.[18,19] GVHD prophylaxis consisted of PTCy on days 3 and 4, mycophenolate mofetil from days 5 to 35, and either tacrolimus or sirolimus from days 5 to either 60, 90, or 180 as previously described.[19-21] Patients receiving their second alloBMT were excluded from this analysis. Potential family members were HLA typed at the HLA-A, HLA-B, HLA-DRB1, HLA-C, and HLA-DQB1 loci at a high-resolution level. Anti-HLA antibodies were checked, and recipients with donor-specific antibodies not amenable to desensitization were excluded. Donors underwent bone marrow (BM) harvest or peripheral blood (PB) mobilization by subcutaneous granulocyte colony stimulating factor at 10 mg/kg per day for 5 days. Unmanipulated BM or PB was infused fresh on day 0.

Outcome definitions

Overall survival (OS) was defined from BMT until death from any cause, censored at the last follow-up date for alive patients.
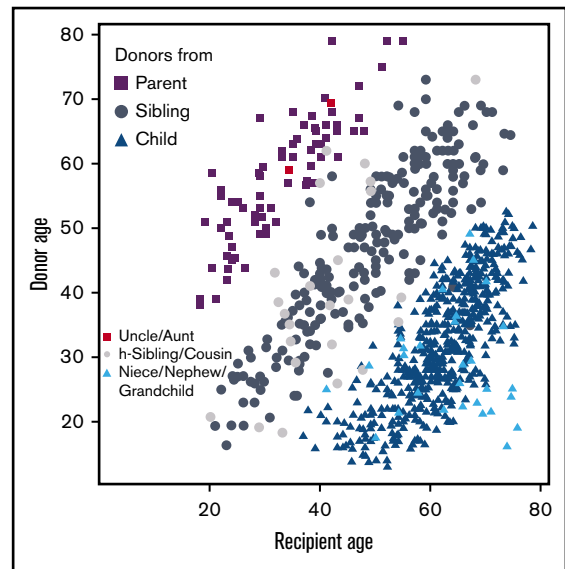

Figure 1. Donor age and relationship correlate with recipient age. Within a given donor-recipient relationship, donor age and recipient age are linearly correlated.

Progression-free survival (PFS) was defined as time from BMT until death from any cause, relapse, or progression, whichever occurred first, censored at the last follow-up date with disease assessment measures. Nonrelapse mortality (NRM) was defined as death in the absence of relapse or progression. Graft failure was defined as <5% myeloid donor chimerism at day 60, or after donor engraftment, subsequent development of 5% donor chimerism in the absence of marrow disease. Relapse and NRM were considered competing risks for one another. Acute graft-versus-host disease (aGVHD) was scored using the modified Keystone Criteria,[22] and chronic graft-versus-host disease (cGVHD) was evaluated by National Institutes of Health Consensus Criteria.[23] Relapse, progression, graft failure, and donor lymphocyte infusions were considered competing events for GVHD. ABO mismatch was defined as major (ie, donor A/recipient O, donor B/recipient O, donor AB/recipient A, B, or O), minor (ie, donor O/recipient A, B, or AB, donor A/recipient AB, donor B/recipient AB), or bidirectional (ie, donor A/recipient B, donor B/recipient A).

Statistical section

The primary goal of this study was to analyze the effect of donor age on clinical outcomes. The distribution of patient age and donor age was explored initially by examining potential nonlinearity relationship with outcome. For OS and PFS, Kaplan-Meier estimates were reported with group differences tested by log-rank tests. For relapse, NRM, and GVHD outcomes, estimates of cumulative incidence function were reported with group differences tested by Gray's test.[24] Given relevant clinical characteristics, prespecified factors included the following: (1) patient age (considered as a continuous variable), (2) disease risk index (DRI) (low, intermediate, and high/very-high risk by Armand criteria[25]) for all outcomes, (3) BMT year (2014 to 2017 vs 2002 to 2013, categorized by median [cutoff based on univariate analysis]), (4) recipient CMV (positive vs negative) adjusted in survival-related outcomes, and (5) graft source (BM vs PB), adjusted in GVHD

Table 1. Recipient characteristics

Characteristic	n	%
Number of patients	889	
Recipient age, median (range), y	59 (18-78.4)	
Donor age, median (range), y	37 (13-79)	
Sex, M/F	566/323	64/36
Diagnosis		
Myeloid		
AML	258	29
Myelodysplastic syndromes	85	10
Chronic myeloid leukemia	30	3
Chronic myelomonocytic leukemia	14	2
Myeloproliferative neoplasm	22	2
Other acute leukemias	18	2
Lymphoid		
Acute lymphoid leukemia	70	8
Chronic lymphocytic leukemia	48	5
Low-grade B-cell lymphoma	77	9
High-grade B-cell lymphoma	136	15
Hodgkin lymphoma	56	7
T-cell lymphoma	43	5
Multiple myeloma	32	4
DRI (n = 881)		
Low	142	16
Intermediate	558	63
High/very high	181	20
HCT-CI (n = 677)		
0	107	12
1-2	261	29
≥3	309	35
CMV status (n = 885)		
Pt neg, donor neg	291	33
Pt pos, donor neg	198	22
Pt neg, donor pos	127	14
Pt pos, donor pos	269	30
ABO compatibility		
Compatible	589	66
Major incompatibility	157	18
Minor incompatibility	143	16
Graft source (n = 886)		
BM	710	80
PB	176	20
Sex mismatch		
Female into male	236	27
No female into male	653	73
Donor/recipient relationship		
Mother	49	6
Father	22	3
Sibling, full	226	25
Sibling, half	16	2

Table 1. (continued)

Characteristic	n	%
Child	537	60
Cousin	8	1
Niece or nephew	22	2
Grandchild	7	1
Uncle	2	0

F, female; M, male; neg, negative; pos, positive; Pt, patient.

outcomes for assessing the donor-age effects. The resultant model was set up through examination of the potential nonlinearity effect of patient age and donor age on OS with the aforementioned adjustments. Our data provided insufficient evidence of nonlinearity effect for patient age ($P = .81$) and donor age ($P = .17$) on OS. Therefore, all the models were fit with both donor age and patient age as linear continuous variables with the above additional adjustments. By assessing the adjusted effect of donor age, Cox proportional hazard models were applied for OS and PFS; Fine and Gray's regression models[26] were applied for relapse, NRM, and GVHD accounting for the corresponding competing events.[27] The hematopoietic cell transplantation comorbidity index[28] (HCT-CI) was available for three-quarters of the cohort. The outcomes were modeled both with and without this variable. In addition, there was statistical evaluation of donor-patient relationship or kinship. A recipient (depending on their age and personal status) could have a child, sibling, or parental donor, and in rare circumstances, second-order donor kinships were also grouped with the corresponding donor-age generations. In most of our cohort, a choice of child donor was limited when patient age ≤40 years (n = 4 outliers), and a choice of parental donor was limited when patient age was ~40 years or older (n = 16 outliers). Thus, the effects of donor kinship were analyzed with the same adjustments as used for donor age effects. We compared use of parental vs sibling donor in patients age ≤40 years, as well as use of child vs sibling donor in patients age >40 years.

All the analyses were generated from R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria), and all the reported P values are 2-sided. P values ≤.05 were considered statistically significant.

Results

Transplant characteristics

There were 889 consecutive adult (age ≥18) patients who received uniform conditioning and GVHD prophylaxis for haplo transplant between 2002 and 2017. The median follow-up was 2.8 years (range: 9 days to 11.4 years) for all patients, based on reverse Kaplan-Meier method; additionally, 46% of patients were followed up completely, and the median follow-up among survivors was 2.5 years after BMT (range: 71 days to 11.4 years). Recipient, donor, and other transplant characteristics are shown in Table 1. The median recipient age was 59 years (range: 18 to 78 years). The recipient age was ≤45 years in 21%, 46 to 65 years in 52%, and >65 years in 27%. The most common diagnosis was B-cell lymphoma, including chronic lymphocytic leukemia (36%) followed by acute myeloid leukemia (AML) (28%), and myelodysplastic syndrome (10%). Most (63%) had intermediate-risk disease by DRI,
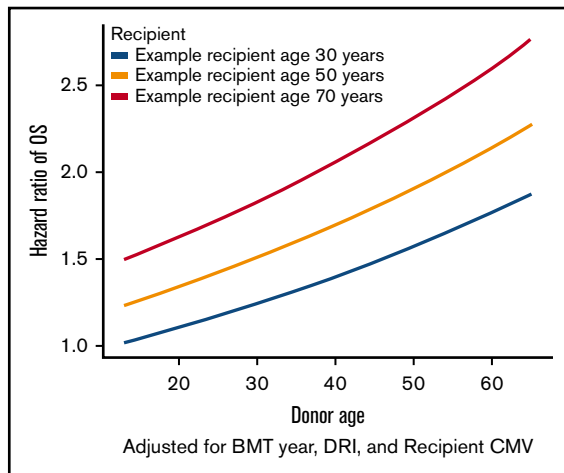
Figure 2. Estimated HR for OS as a function of donor age for 3 values of hypothetical recipient age. (Example recipients ages 30 years [blue], 50 years [orange], and 70 years [red].) HRs were estimated from the fitted multivariable Cox model for OS regressed against donor age, patient age, DRI, BMT year, and CMV status. This shows the calculated the relative hazard of OS for 3 example recipients with ages of 30, 50, and 70, as a continuous function of donor age. Each example recipient shows a higher risk of mortality when older donor is used (HR = 1.13 [95% confidence interval: 1.04-1.21], $P = .002$ per decade of donor age increase).

whereas 20% were high/very high. The median donor age was 37 years (range: 13 to 79 years). Donor relationship was sibling in 25%, parent in 8%, child in 60%, and second- or third-degree relative in 6%. Donor relationship is biologically tied to recipient age, as shown in Figure 1. The median difference in patient age compared with donor age was 24.9 years (interquartile range 3.4, 31). Supplemental Figure 1 shows the relative difference in patient and donor ages. The overall incidence of graft failure in our entire patient cohort was 5.5%, with an additional 1.7% of patients dying before engraftment could be assessed by chimerism.

OS and PFS

The initial analyses were performed on just the 834 first-degree related donors, because of the small numbers of second- and third-degree related donors (6%). The 3-year OS and PFS rates for our study cohort were 54% (95% confidence interval [CI]: 50% to 57%) and 41% (95% CI: 37% to 44%), respectively. The Cox proportional hazard ratios (HRs) for OS and PFS were initially determined by univariate analysis (supplemental Table 1). In our cohort, the risk of mortality increased with donor age and patient age (Figure 2) after prespecified adjustments. We fitted a Cox model for OS regressed against donor

age, patient age, DRI, BMT year, and CMV status. We then took the estimated model coefficients and calculated the relative hazard of OS for 3 "hypothetical" example patients with ages of 30, 50, and 70 years, as a continuous function of donor age. Specifically, donor age increasing by decade was associated with poorer OS (HR, 1.13 [1.04, 1.21; $P = .002$]) and worse PFS (HR, 1.08 [1.01, 1.16; $P = .022$]) (Table 2; supplemental Table 1). With only age stratified, the effect of categorized donor age (by quartile approximation) for both OS and PFS was consistent across patient age groups, age <45 years, 46 to 65 years, and >65 years (Figure 3). The results remained unchanged when the 55 second- and third-degree relatives (grandchildren/niece/nephew, n = 29, and first cousins/half sibling, n = 24, and an uncle and aunt) were included.

NRM and relapse

The 3-year cumulative incidence of relapse and NRM was 46% (95% CI: 43% to 50%) and 13% (95% CI: 11% to 16%). Increasing donor age by a decade was associated with poorer NRM (subdistribution hazard ratio [SDHR], 1.19 [1.05 to 1.34]; $P = .006$). However, increasing donor age did not appear to impact relapse (SDHR, 1.03 (0.95 to 1.11; $P = .47$) (Table 2; supplemental Table 2; supplemental Figure 2).

Graft failure and GVHD

Figure 4 shows the graft failure rate assessed by patient-donor age. There were increasing rates of graft failure with increasing age overall, although it was not statistically significant. P values tested the correlations between donor age group and graft failure rate in each age cohort.

The 100-day cumulative incidence of grade 2 to 4 aGVHD and grade 3 to 4 aGVHD was 27% (95% CI: 24% to 30%) and 5% (95% CI: 4% to 7.4%). The 2-year cumulative incidence of cGVHD was 16% (95% CI: 14% to 19%). Figure 5 shows the cumulative incidence of GVHD by patient age and donor age. Multivariable analysis (Table 2; supplemental Table 3) shows a higher risk for both grade 2 to 4 (SDHR, 1.11 [1.03, 1.21]; $P = .011$) and grade 3 to 4 GVHD (1.27 [1.04, 1.54]; $P = .019$) with increasing donor age per decade, but not for cGVHD (SDHR, 1.02 [0.91, 1.15]; $P = .74$). There was no difference in any outcome with either tacrolimus or sirolimus use. The incidence of limited cGVHD was 8.0% and 6.0% of extensive cGVHD. Neither limited nor extensive cGVHD showed a statistically significant difference between donor age groups in the entire cohort, or when stratified by recipient's age (supplemental Table 3).

Donor relationships/kinship

We examined sex mismatch, and it had no impact on the outcomes (supplemental Table 1). In order to have sufficient numbers of

Table 2. Multivariable analysis for donor age effect and donor kinship effects

| HR/SDHR (95% CI), P	Donor age (per 10 y)	Within age ≤40, parent vs sibling	Within age >40, child vs sibling
OS	1.13 (1.04-1.21), $P = .002$	1.78 (1.01-3.13), $P = .046$	0.89 (0.78-1.03), $P = .11$
PFS	1.08 (1.01-1.16), $P = .022$	1.72 (1.06-2.79), $P = .029$	0.94 (0.83-1.06), $P = .30$
Relapse	1.03 (0.95-1.11), $P = .47$	1.50 (0.88-2.54), $P = .13$	1.01 (0.77-1.33), $P = .92$
NRM	1.19 (1.05-1.34), $P = .006$	1.28 (0.46-3.51), $P = .64$	0.64 (0.39-1.03), $P = .07$
Grade 2 to 4 aGVHD	1.11 (1.03-1.21), $P = .011$	0.89 (0.46-1.72), $P = .73$	0.67 (0.49-0.92), $P = .013$
Grade 3 to 4 aGVHD	1.27 (1.04-1.54), $P = .019$	0.81 (0.21-3.09), $P = .76$	0.30 (0.15-0.61), $P < .001$
cGVHD	1.02 (0.91-1.15), $P = .74$	1.01 (0.35-2.88), $P = .99$	0.74 (0.48-1.14), $P = .17$
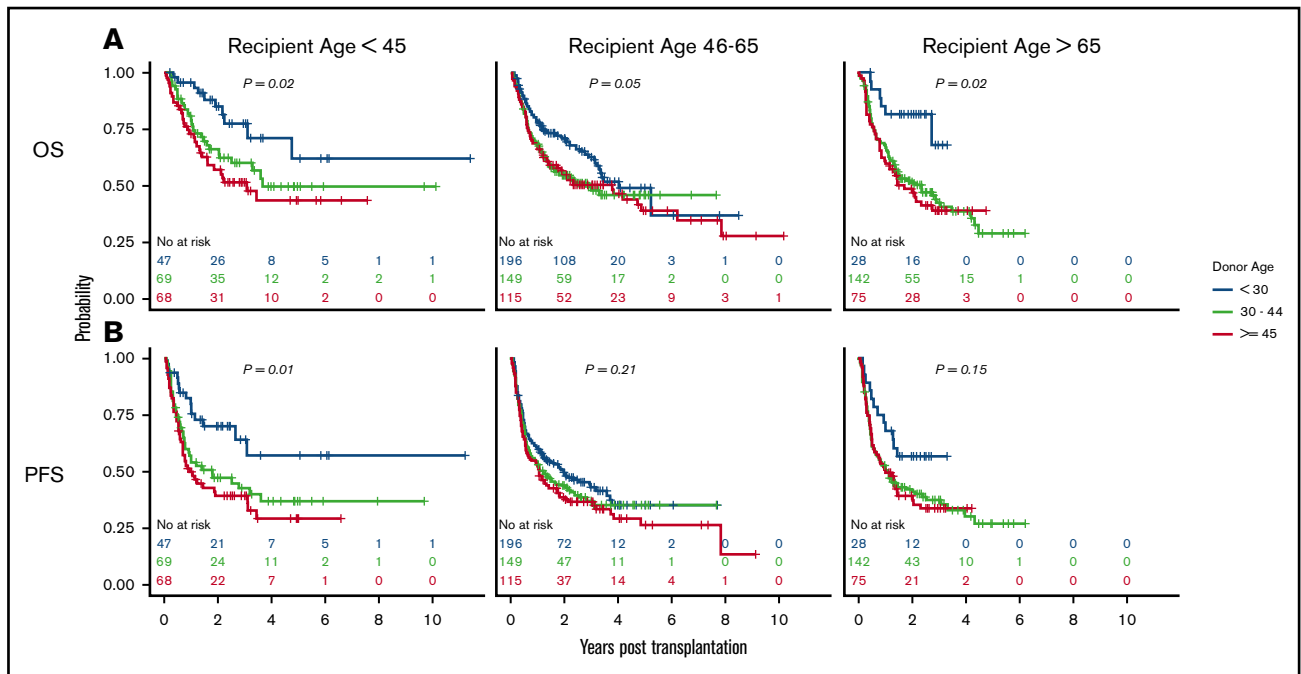
Figure 3. OS and PFS. Kaplan-Meier curves by categorical groups of recipient age and donor age for OS (A) and PFS (B). *P* values were based on log-rank tests (*P* = .27 for OS and *P* = .29 for PFS). Recipients with younger donors showed OS/PFS benefits when compared with recipients with elder donors.

donors to assess parental donors vs siblings, we looked at patients younger than 40 (n = 71). Parental donors were associated (although not significantly because of small number of events) with inferior outcomes compared with sibling donors. No significant differences were observed between maternal and paternal donors (supplemental Table 2; supplemental Figure 3).

Discussion

The BMT field continuously seeks to identify, and when possible, modify factors that could improve recipient outcomes after alloBMT. There can be little doubt concerning the role of patient characteristics on BMT outcomes,[7,18] but many of these features, such as patient age and clinical status, cannot be easily modified.

With the diminished reliance on matched sibling donors, especially with the increasing evidence for the safety and effectiveness of mismatched donors,[4,7,12] modifiable donor characteristics have become an increasing area of interest. Most patients now have several potential donors available.[5,18-20,29,30] Various donor characteristics, including degree of HLA match, age, sex, parity, CMV serostatus, and ABO, have been reported to influence survival after alloBMT.[13] In the largest analysis on the subject, donor age and HLA disparity were the only donor characteristics that influenced the outcome of unrelated donor alloBMT using modern transplant platforms.[13] The effects of donor age on alloBMT outcomes have been confirmed in several other studies as well.[13,14,31,32]
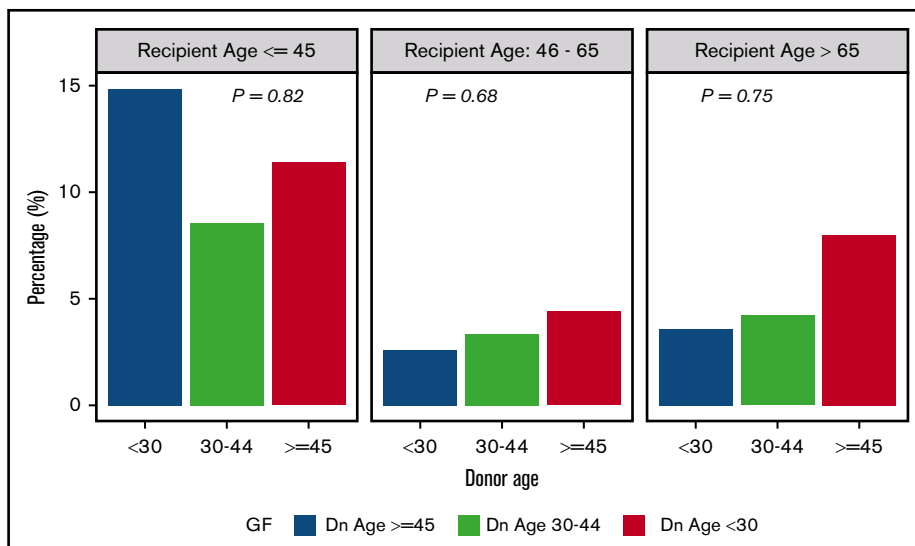

Figure 4. Percentage of graft failure (GF) and death before chimerism assessment (Died) by donor age (Dn Age) group for each age group. No statistically significant association was observed between graft failure and donor age at each age group, although the percentage of graft failure/death before chimerism assessment was quantitatively higher in donor age >30 group when recipient's age >46 years.
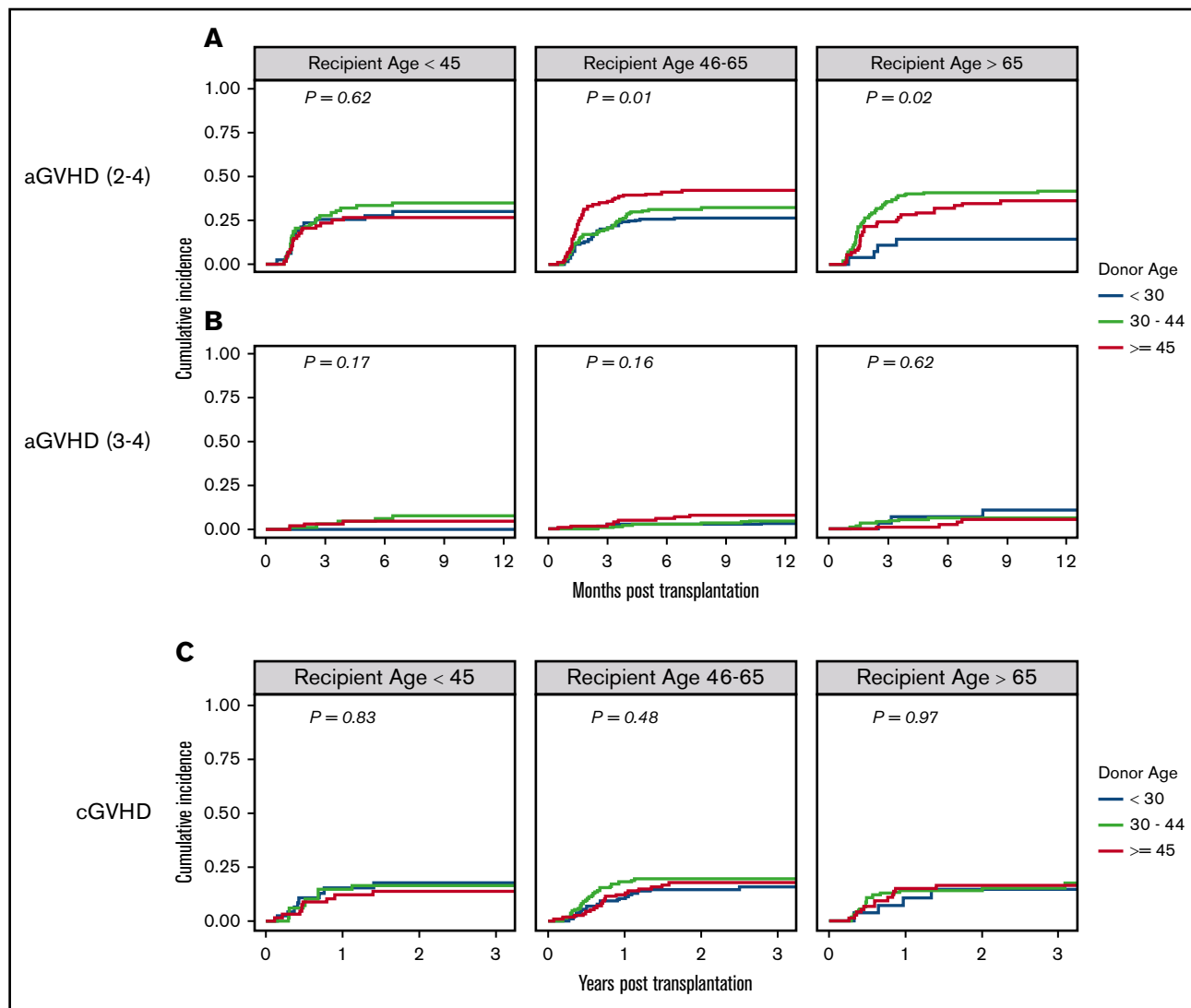
Figure 5. GVHD. Cumulative incidence of GVHD by recipient age and donor age: grade 2 to 4 aGVHD (A); grade 3 to 4 aGVHD (B); and cGVHD (C).

We also found that increasing donor age was the only donor characteristic that influenced OS and PFS after NMA haplo alloBMT with PTCy. Donor sex, ABO matching, and CMV status did not influence OS or PFS in multivariable analyses. We[33] and others[34,35] previously showed that degree of HLA match did not influence outcomes after haplo alloBMT with PTCy. As expected, patient characteristics, including age and DRI, and year of transplant also influence OS and PFS. There is a significant impact of patient comorbidities on transplant outcomes, especially in the older population. In our cohort, 76% of patients (n = 677) had HCT-CI data tabulated. In the multivariable analyses for patients in whom this information was available, there was no significant association between HCT-CI and the clinical outcomes nor change in the effect of donor age with or without the inclusion of the HCT-CI (supplemental Table 4). DRI does remain a significant predictor for survival and relapse with or without HCT-CI in the model, suggesting the disease biology may supersede patient factors with this specific transplant platform.

However, younger donors appear to be associated with improved outcomes, regardless of patient age or DRI. Although not statistically

significant, higher rates of graft failure with increasing age were observed. One could hypothesize that this is due to lower stem cell yield in the collections with decreasing cellularity with advancing age or it may suggest a role for increased clonal hematopoiesis in the donors contributing to more graft failure.

Our results here also showed increasing donor age was associated with increased NRM and aGVHD but did not influence relapse. A recent analysis from 8 transplant centers in Italy similarly found that younger donors appeared to reduce the incidence of aGVHD and NRM, while increasing the risk of relapse with no effect on OS or PFS. The differences may be related to the heterogeneity of the transplant platforms, including conditioning intensity, in the Italian review, or that there was no adjustment for patient age. In our patients, and perhaps theirs, patient age and donor age were inversely correlated (Figure 1), which could obscure any effect of younger donor age on outcome if this is not taken into account. In addition, our study's lack of effect of donor age on relapse risk could be explained by the fewer patients with high/very high DRI as well as fewer PB transplants. Other variables that were not examined could have influenced the results.

Unlike HLA-matched related and HLA-matched unrelated donor alloBMT, where there will be no effect of donor relationship/kinship, haplo donors may be siblings, parents, children, cousins, nieces, nephews, aunts, uncles, or grandchildren (Figure 1). Thus, the young donors available will represent different kinships depending on the recipient's age (Figure 1) and could be a confounder. For recipients <35, younger donors were usually siblings; whereas for older recipients, donors were usually children. Our data did find the children donors were associated with better outcomes than parental donors. These positive effects of younger donor age were consistent, regardless of the recipient age and kinship. The recent Italian analysis of haplo donors and PTCy also suggested that children should be chosen over parents as donors, but also found that maternal donors may be associated with worse survivals than paternal.[12] Our study with small numbers of parental donors did not demonstrate a difference in outcomes between maternal and paternal donors. Furthermore, we did not demonstrate a difference for female into male transplants.

At Johns Hopkins, we currently implement a donor selection algorithm based on these real-world results (supplemental Table 5). We prioritize the choice of the youngest adult-sized donor where feasible and medically appropriate. We do not prioritize based on degree of HLA match or degree of kinship. Although donor ABO, CMV, and sex did not appear to influence outcomes in our analysis or with unrelated donors,[13] we do avoid ABO major mismatches because they require red cell reduction, and major ABO incompatibility can be associated with prolonged red cell transfusion requirements.[36] Similarly, we only prioritize CMV matches when everything else is equal, based on European Group for Blood and Marrow Transplant data with unrelated donors.[37] Finally, the Center for International Blood and Marrow Transplant Research found that haplo PB allografts were associated with more GVHD even in the setting of PTCy,[38] and we saw a similar trend. Thus, we prioritize BM in all diseases except those like MDS or myeloproliferative disorders where graft failure can be relatively higher or leukemias

with presence of MRD where relapses are high. Our results in B-cell lymphomas,[39] MRD-negative AML,[40] and MRD-negative ALL,[41] especially with posttransplant maintenance approaches, show >70% OS rate with use of BM allografts; thus, we are unwilling to assume the higher risk of GVHD for those diseases.

In conclusion, we found that older donors were associated with inferior OS and PFS after NMA haplo BMT with PTCy in adult patients, similar to what has been reported for unrelated donors.[13] These data strongly suggest that the youngest available adult-sized donors, usually a young sibling or even a second-degree relative (grandchild, niece, or nephew), should be preferred when multiple haplo donors are available.

Acknowledgments

Authorship

Contribution: A.E.D., C.F., and R.J.J. were involved in conception and design, data collection, data analysis and interpretation, and manuscript writing and revisions; H.-L.T. and R.V. were involved in the conception and design, statistically analyzed and interpreted the data, and assisted in manuscript revisions; P.H.I. and K.R.C. were involved in data collection, manuscript writing, and revisions; and all authors approved the manuscript.

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