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Increasing Use of Allogeneic Hematopoietic Cell Transplantation in Patients Aged 70 Years and Older in the United States

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Regular Article

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TRANSPLANTATION

Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States

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Key Points

- Over the last decade, allogeneic HCT has been increasingly administered in the United States to adults aged 70 and older with hematologic malignancies.

- Allogeneic transplant outcomes were reasonable; high comorbidity and ablative conditioning regimens were associated with inferior outcomes.

In this study, we evaluated trends and outcomes of allogeneic hematopoietic cell transplantation (HCT) in adults ≥70 years with hematologic malignancies across the United States. Adults ≥70 years with a hematologic malignancy undergoing first allogeneic HCT in the United States between 2000 and 2013 and reported to the Center for International Blood and Marrow Transplant Research were eligible. Transplant utilization and transplant outcomes, including overall survival (OS), progression-free survival (PFS), and transplant-related mortality (TRM) were studied. One thousand one hundred and six patients ≥70 years underwent HCT across 103 transplant centers. The number and proportion of allografts performed in this population rose markedly over the past decade, accounting for 0.1% of transplants in 2000 to 3.85% (N = 298) in 2013. Acute myeloid leukemia and myelodysplastic syndromes represented the most common disease indications. Two-year OS and PFS significantly improved over time (OS: 26% [95% confidence interval (CI), 21% to 33%] in 2000-2007 to 39% [95% CI, 35% to 42%] in 2008-2013, $P < .001$; PFS: 22% [16% to 28%] in 2000-2007 to 32% [95% CI, 29% to 36%] in 2008-2013, $P = .003$). Two-year TRM ranged from 33% to 35% and was unchanged over time ($P = .54$). Multivariable analysis of OS in the modern era of 2008-2013 revealed higher comorbidity by HCT comorbidity index ≥3 (hazard ratio [HR], 1.27; $P = .006$), umbilical cord blood graft (HR, 1.97; $P = .0002$), and myeloablative conditioning (HR, 1.61; $P = .0002$) as adverse factors. Over the past decade, utilization and survival after allogeneic transplant have increased in patients ≥70 years. Select adults ≥70 years with hematologic malignancies should be considered for transplant. (*Blood*. 2017;130(9):1156-1164)

Introduction

Allogeneic hematopoietic cell transplantation (HCT) offers the best potential for prolonged disease control for many hematologic malignancies. Historically, older adults were not considered candidates out of concern for increased toxicity and mortality,[1] thus excluding the majority of hematologic malignancy patients who may have gained benefit. In recent years, the development of reduced-intensity conditioning (RIC) and nonmyeloablative (NMA) regimens,[2] coupled with improvements in supportive care measures[3] and more accurate HLA typing methods,[4] has broadened the application of HCT to include older adults. As such, 22% of HCT recipients for malignant diseases from 2007 to 2013 reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) were >60 years of age.[5]

The feasibility of HCT in adults >50 years of age, and even those >65 years, has been detailed in several reports.[6-11] In a registry analysis of patients with acute myeloid leukemia (AML) in first remission or myelodysplastic syndrome (MDS) receiving RIC allogeneic transplants, no significant differences in outcomes were uncovered among HCT recipients aged 40 to 50 years versus those >65 years.[7] Similar results have been reported in multicenter series from the United States and the European Society for Blood and Marrow Transplantation, where disease status and medical comorbidities, rather than chronological age, appear to predict for outcomes.[6,8,11]

Although most studies conclude that older age alone should not preclude transplant, very limited data exist regarding patients transplanted in their eighth decade.[12] This population is of particular interest, as it has been shown that for each 5-year increase in age beyond 65 years, the proportion of cancer patients with comorbidity, disability, and/or geriatric syndromes increases by 3% to 5%,[13,14] prompting recommendations to perform a comprehensive geriatric assessment for all cancer patients in this age group.[15] Further, as the population continues to age, with 50% of all cancers and 70% of cancer mortality occurring in adults ≥65 years, the number of patients considered for HCT in their eighth decade will continue to rise.[16]

We therefore conducted an observational study of allogeneic HCT recipients ≥70 years reported to the CIBMTR between 2000 and 2013 with the aims of describing transplant utilization as well as baseline characteristics, outcomes, and prognostic factors for this understudied cohort of HCT recipients.

Methods

Data sources

The CIBMTR is a research collaboration between the National Marrow Donor Program/Be The Match and the Medical College of Wisconsin. The CIBMTR represents an international network of transplant centers that submit transplant-related data for patients. It has been collecting HCT outcomes data for >40 years and has an extensive database of detailed patient-, transplant-, and disease-related information with prospectively collected longitudinal data.[17] CIBMTR data are collected in compliance with Health Insurance Portability and Accountability Act regulations and with all applicable federal regulations pertaining to the protection of human research participants, as determined by a continuous review by the National Marrow Donor Program institutional review board and the Medical College of Wisconsin.

The CIBMTR collects 2 levels of data: registration-level data are retrieved from Transplant Essential Data forms, and additional research level data are collected using Comprehensive Report Forms (CRFs). The latter is a subset of the former; patients for whom CRF-level data are collected are chosen through a selection algorithm, as these forms are longer and require more extensive data, including detailed disease information. Thus, the objective of this study included assessing transplant practices and activity in the United States using Transplant Essential Data–level data. Additional analysis with more detailed disease-specific information was performed in a subset of this population as described in statistical section below.

Patient population

Patients aged ≥70 years at time of first allogeneic HCT occurring between 2000 and 2013 and reported to the CIBMTR were included. Exclusion criteria included syngeneic donor transplant and patients reported to the CIBMTR who received HCT outside of the United States.

Definitions and outcomes

Disease status at time of transplant followed CIBMTR disease risk classification[18]: early disease (acute leukemia in first complete remission, myelodysplastic syndromes with <5% blasts, or chronic-phase chronic myeloid leukemia [CML]), intermediate disease (second or greater complete remission acute leukemia, accelerated-phase CML), and advanced disease (acute leukemia not in remission, myelodysplastic syndromes with ≥5% marrow blasts, or blast-phase CML); lymphomas were classified according to chemotherapy sensitivity (sensitive or resistant at time of transplant). Patients with AML were also described in greater detail using CRF data to report disease characteristics of interest, including frequency of favorable, intermediate, and poor cytogenetic categories and presence or absence of FLT3 mutations. Conditioning regimen intensity followed CIBMTR working definitions (myeloablative vs RIC/NMA)[19,20]; due to data capture constraints, RIC and NMA were grouped together. Comorbidity was scored using the HCT comorbidity index; recipient HCT-comorbidity index scores have been routinely reported to the CIBMTR on all allogeneic HCT recipients since 2008. Performance status was captured by the Karnofsky Performance Scale (KPS). Disease Risk Index (DRI)[21] was evaluated in the entire population and categorized in a subset of patients with all available elements. HLA-matched unrelated donors required 8/8 matching at HLA-A, HLA-B, HLA-C, and HLA-DRB1 at high resolution. Mismatched related donors included haploidentical donors as well as single-antigen and allele mismatches
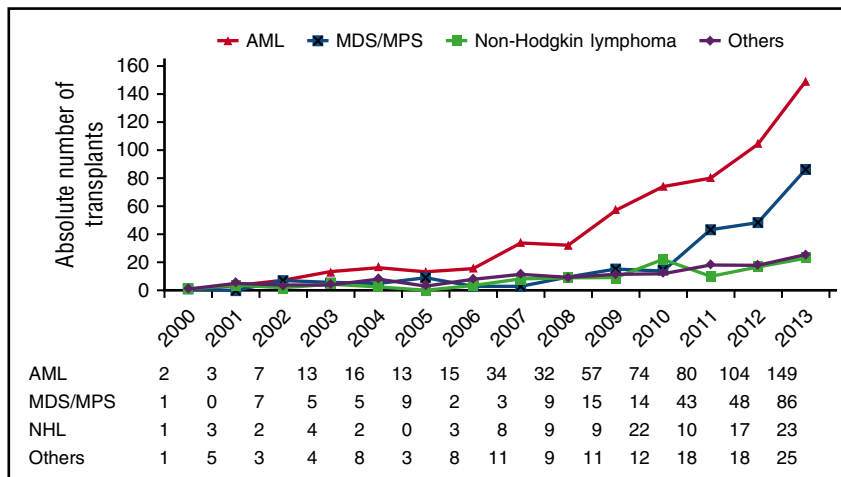
Figure 1. Annual number of HCTs in patients 70 years and older by indication. MPS, myeloproliferative syndrome.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
AML	2	3	7	13	16	13	15	34	32	57	74	80	104	149
MDS/MPS	1	0	7	5	5	9	2	3	9	15	14	43	48	86
NHL	1	3	2	4	2	0	3	8	9	9	22	10	17	23
Others	1	5	3	4	8	3	8	11	9	11	12	18	18	25

(ie, 7 of 8). Neutrophil engraftment was defined as neutrophil count above 500/μL for 3 consecutive days. Graft-versus-host disease (GVHD) was defined as acute GHVD (grades II-IV or III-IV according to maximum organ stage) or chronic GVHD.

The primary outcome for this study was overall survival (OS), defined as death from any cause; patients for whom death was not observed were censored at the time of last follow-up. Transplant-related mortality (TRM) was defined as death in the absence of disease relapse or progression. The composite end point of progression-free survival (PFS) required either disease relapse or progression or death; patients alive without such events were censored at the time of last follow up. Primary cause of death for each patient was reported by the treating center.

Statistical analysis

Descriptive statistics summarized the baseline patient, disease, and transplant-related characteristics according to two time cohorts during the study period (2000 to 2007, 2008 to 2013). The proportion of transplants performed in patients 70 years of age and older relative to all transplants performed in the United States was computed. Univariate summary measures for all outcomes were calculated and compared over the two time periods. Probabilities of OS and PFS were calculated using the Kaplan-Meier estimator, and comparisons between groups were performed using log-rank and point-wise tests. Probabilities of neutrophil engraftment, GVHD, TRM, and disease relapse/progression were calculated by cumulative incidence function accounting for competing risks. Comparisons of cumulative incidence across time cohorts were performed via Gray's test.

Prognostic factor analysis was performed on 3 patient subsets. The first analysis included all patients ≥70 years transplanted between 2008 and 2013 with the intention of focusing on a contemporary cohort of patients with all disease indications who received comorbidity assessment by the HCT-comorbidity index (which was not available prior to 2008). For this subset, a multivariable Cox proportional hazards regression model was built using stepwise variable selection to evaluate patient, disease, and transplant variables associated with OS. The variables analyzed were age (70-74 and ≥75 years), gender, HCT-comorbidity index (0-2 and ≥3),[22] KPS (modeled at ≥80% and ≥80%), disease, disease status, donor type (HLA-matched sibling, HLA-mismatched related, and HLA matched unrelated donor, divided according to donor age [<30 and ≥30 years] or mismatched unrelated donor, unrelated donor with HLA-matching unknown, and umbilical cord blood), conditioning regimen intensity[19,20] graft source (bone marrow, mobilized peripheral blood stem cells, and umbilical cord blood), year of transplant, donor-recipient gender match, donor–recipient cytomegalovirus serologic status, and GVHD prophylaxis (calcineurin inhibitor and methotrexate, calcineurin inhibitor and mycophenolate mofetil, and calcineurin inhibitor with other combinations and other regimens).

The second subset analysis explored variables associated with OS and TRM among patients ≥70 years with controlled disease entering transplant. This subset included patients with early or intermediate-risk AML (ie, patients in complete remission 1 [CR1] or CR2 as opposed to active disease), MDS with <5% blasts, and chemosensitive non-Hodgkin lymphoma (NHL) who

underwent HCT between 2008 and 2013. This more homogenous subset included the most common disease indications for HCT among older adults and enabled analysis of variables associated with TRM without confounding from less common transplant disease indications. Multivariable Cox regression models were constructed by testing the covariates as above with the exception of disease status as all patients in this subset had early or intermediate disease at transplant.

The third subset focused on exploring outcomes by comorbidity and disease status in patients with AML and MDS undergoing transplant between 2008 and 2013. For this subset, probabilities of OS and TRM were calculated as above.

For multivariable analysis performed in the first and second subsets, all covariates associated with outcome at $P < .05$ were retained in the final models and considered significant. Tests of proportionality for each covariate and of interaction between covariates were performed; no violations of proportionality or significant interactions were found. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

Results

HCT utilization for adults 70 years and older over time

A total of 1106 patients ≥70 years underwent first allogeneic HCT in the United States and were reported to the CIBMTR between 2000 and 2013. The absolute number of transplants for adults ≥70 years increased substantially over that time, from 5 in 2000 to 283 in 2013. The proportion of allogeneic HCT recipients ≥70 years also increased over time, from 0.1% in 2000 to 3.85% in 2013. Further, the absolute number of transplant programs performing allogeneic HCT in patients ≥70 years increased from 65 centers in 2000-2007 to 93 centers in 2008-2013. Transplant for AML and MDS accounted for the main indications across time periods (Figure 1).

Patient and HCT characteristics

Baseline patient demographics and transplant characteristics stratified by HCT time period for all patients in the dataset are described in Table 1. The median age at time of HCT was 72 (range, 70-84 years). KPS was <80% in 9% of the patients. Comorbidity by HCT-comorbidity index (captured for recipients transplanted from 2008 to 2013) demonstrated high HCT-comorbidity index of ≥3 in 46% of patients; 16% had HCT-comorbidity index scores of ≥5. Among patients with available DRI, the majority received transplant with intermediate risk. The donor source shifted from related donors in 51% in the initial time period to 70% unrelated grafts in the later time period,

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BLOOD, 31 AUGUST 2017 · VOLUME 130, NUMBER 9

ALLOGENEIC HCT IN ADULTS 70 YEARS AND OLDER 1159

Table 1. Demographics of patients 70 years and older who received HCT from 2000 to 2013

	2000-2007, n (%)	2008-2013, n (%)	All patients, n (%)
No. of patients	207	899	1106
No. of centers	65	93	103
Age at transplant, y			
Median (range)	72 (70-83)	72 (70-84)	72 (70-84)
70-74	176 (85)	807 (90)	983 (89)
75-79	27 (13)	88 (10)	115 (10)
≥80	4 (2)	4 (<1)	8 (1)
Sex			
Male	151 (73)	629 (70)	780 (71)
Female	56 (27)	270 (30)	326 (29)
KPS			
<80%	17 (8)	87 (10)	104 (9)
≥80%	119 (57)	784 (87)	903 (82)
Missing	71 (34)	28 (3)	99 (9)
HCT-comorbidity index			
0	—	248 (28)	248 (22)
1-2	—	234 (26)	234 (21)
≥3	—	417 (46)	417 (38)
Missing*	207	0	207 (19)
Disease			
AML	103 (50)	496 (55)	599 (54)
ALL	2 (<1)	23 (3)	25 (2)
CLL/PLL	22 (11)	54 (6)	76 (7)
CML	5 (2)	6 (<1)	11 (<1)
MDS/MPS	32 (15)	215 (24)	247 (22)
Other acute leukemia	1 (<1)	8 (<1)	9 (<1)
NHL	23 (11)	90 (10)	113 (10)
Plasma cell disorder/multiple myeloma	10 (5)	2 (<1)	12 (1)
Other malignancies	3 (1)	0	3 (<1)
Severe aplastic anemia	4 (2)	5 (<1)	9 (<1)
PNH	2 (1)	0	2 (<1)
Disease status			
Early disease	45 (22)	355 (39)	300 (27)
Intermediate disease	25 (12)	93 (10)	118 (11)
Advanced disease	48 (23)	230 (26)	278 (25)
NHL sensitive	10 (5)	79 (10)	89 (9)
NHL resistant	6 (3)	10 (1)	16 (1)
Other (unknown/missing/NA)	73 (35)	132 (15)	205 (19)
DRI†			
Low	6 (3)	32 (4)	38 (3)
Intermediate	28 (14)	152 (17)	180 (16)
High	20 (10)	115 (13)	135 (12)
Very high	7 (3)	18 (2)	25 (2)
Other (missing/NA)	146 (71)	582 (65)	728 (66)
Donor type			
Matched related	93 (45)	204 (23)	297 (27)
Mismatched related	13 (6)	67 (7)	80 (7)
Matched unrelated	52 (25)	463 (52)	515 (47)
Mismatched unrelated	12 (6)	68 (8)	80 (7)
Unrelated HLA match unknown	20 (10)	46 (5)	66 (6)
Umbilical cord blood	7 (3)	51 (6)	58 (5)
Missing	10 (5)	0	10 (1)
Unrelated donor age, median (range), y	36 (21-60)	30 (19-61)	31 (19-61)
18-30	23 (27)	278 (48)	301 (46)
31-40	24 (29)	139 (24)	163 (25)
41-50	21 (25)	96 (17)	117 (18)
51-61	5 (6)	25 (4)	30 (5)
Unknown	11 (13)	39 (7)	50 (8)
Graft source			
Bone marrow	17 (8)	93 (10)	110 (10)
Peripheral blood	183 (88)	755 (84)	938 (85)
Umbilical cord blood	7 (3)	51 (6)	58 (5)

Table 1. (continued)

	2000-2007, n (%)	2008-2013, n (%)	All patients, n (%)
Donor–recipient sex match			
Male–male	95 (46)	388 (43)	483 (44)
Male–female	25 (12)	154 (17)	179 (16)
Female–male	50 (24)	203 (23)	253 (23)
Female–female	30 (14)	98 (11)	128 (12)
Unknown	7 (3)	56 (6)	63 (6)
Donor–recipient CMV status			
Positive–positive	16 (8)	269 (30)	285 (26)
Positive–negative	7 (3)	67 (7)	74 (7)
Negative–positive	37 (18)	292 (32)	329 (30)
Negative–negative	13 (6)	176 (20)	189 (17)
Unknown	134 (65)	95 (11)	229 (21)
Regimen intensity			
Ablative	11 (5)	102 (11)	113 (10)
RIC/NMA	178 (86)	796 (89)	974 (88)
Unknown	18 (9)	1 (<1)	19 (2)
Conditioning regimen			
Flu/Bu ± other	29 (14)	368 (41)	397 (36)
Flu/Mel ± other	35 (17)	137 (15)	172 (16)
Flu/TBI ± other	65 (31)	274 (30)	339 (31)
Bu based	11 (5)	17 (2)	28 (3)
Flu/Cy ± other	26 (13)	40 (4)	66 (6)
TBI/TLI ± other	16 (8)	49 (5)	65 (6)
Other	17 (8)	14 (2)	31 (3)
Unknown	8 (4)	0	8 (<1)

ALL, acute lymphoblastic leukemia; Bu, busulfan; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; Flu/Bu, fludarabine + busulfan; Flu/Mel, fludarabine + melphalan; Flu/TBI, fludarabine + total body irradiation; MPS, myeloproliferative syndrome; NA, not available; PLL, prolymphocytic leukemia; PNH, paroxysmal nocturnal hemoglobinuria; Flu/Cy, fludarabine + cyclophosphamide; TBI/TLI, total body irradiation or total lymphoid irradiation.

*HCT-comorbidity index was not captured by the CIBMTR registry prior to 2008.

†All elements required to generate the DRI were not available in all patients.

driven mostly be greater use of matched unrelated donors over time. Although most patients received RIC/NMA conditioning regimens, myeloablative regimens were administered to 10% overall. The more widespread use of fludarabine plus busulfan–based regimens signified the largest change in conditioning regimens over time. Increasing numbers of patients entered transplant with controlled disease in the more recent time period.

Supplemental Table A (available on the *Blood* Web site) includes additional disease and transplant-related details regarding AML patients transplanted between 2008 and 2013. In this subset of 120 patients with AML with available information, 70% had intermediate cytogenetics, 85% of patients with available FLT3 status were wild-type, and 69% were in morphologic complete remission at time of transplant.

Outcomes

Unadjusted 1- and 2-year transplant outcome probabilities (neutrophil engraftment, grades II-IV and III-IV acute GVHD, chronic GVHD, TRM, relapse/progression, PFS, and OS) stratified by HCT time period are summarized in Table 2. Two-year PFS improved significantly from 2000-2007 to 2008-2013 (22% [95% confidence interval (CI) 16% to 28%] vs 32% [29% to 36%], $P = .003$), while TRM remained static ($P = .54$ over the entire time period. Two-year OS also improved significantly over time, from 26% [95% CI, 21% to 33%] in 2000-2007% to 39% [95% CI, 35% to 42%] in 2008-2013, $P < .001$ (Figure 2A). Overall and disease-free survival among patients with the most common indications for HCT from 2008 to 2013 and according to DRI in the same period are shown in Figure 2B-E).

Table 2. Univariate analysis of posttransplant outcomes of patients aged 70 years and older and recipients of an allogeneic HCT from 2000 to 2013

	Total cohort prob. (95% CI)	2000-2007 prob. (95% CI)	2008-2013 prob. (95% CI)	P*
Neutrophil engraftment†				
No. evaluated	—	—	890	—
28 d	—	—	92 (90-93)	—
Acute GVHD, grade II-IV				
No. evaluated	427	105	322	.63
100 d	32 (28-37)	31 (23-41)	33 (28-38)	.82
Acute GVHD, grade III-IV				
No. Evaluated	427	105	322	.05
100 d	13 (10-17)	18 (11-26)	12 (9-16)	.13
Chronic GVHD				
No. evaluated	1025	161	864	.94
1 y	32 (30-35)	32 (25-40)	32 (29-36)	.97
2 y	37 (34-40)	35 (28-43)	38 (35-41)	.55
TRM				
No. evaluated	1086	192	894	.77
1 y	25 (23-28)	26 (20-33)	25 (22-28)	.73
2 y	33 (30-36)	35 (28-42)	33 (29-36)	.54
Relapse/progression				
No. evaluated	1086	192	894	.04
1 y	32 (30-35)	38 (31-45)	31 (28-34)	.09
2 y	37 (34-40)	43 (36-50)	35 (32-38)	.04
PFS				
No. evaluated	1086	192	894	.001
1 y	42 (39-45)	36 (29-43)	44 (40-47)	.04
2 y	30 (27-33)	22 (16-28)	32 (29-36)	.003
OS				
No. evaluated	1106	207	899	<.001
1 y	50 (47-53)	42 (35-49)	52 (49-56)	.007
2 y	36 (33-39)	26 (21-33)	39 (35-42)	<.001

Prob., probability.

*P value for significance between the 2000-2007 and 2008-2013 cohorts.

†Neutrophil engraftment was not consistently captured prior to 2008.

The most frequent primary cause of death was relapse/progression of primary disease, which accounted for 46% of deaths. Infection and GVHD were each reported as the primary cause of death in 10%. Cause of death could not be clarified in 22% of the patients.

Prognostic factor analysis in modern cohorts

The first subset analysis focused on all patients ≥70 years transplanted between 2008 and 2013. Significant prognostic factors for inferior survival included high comorbidity defined by HCT-comorbidity index ≥3 (hazard ratio [HR], 1.27; 95% CI, 1.07-1.51; $P = .006$), receipt of cord blood as a donor source (HR, 1.97; 95% CI, 1.37-2.82; $P = .0002$) relative to HLA matched sibling donor, and use of a myeloablative conditioning regimen (HR, 1.61; 95% CI, 1.25-2.08; $P = .0002$) (Table 3). All other variables tested in the model, including age, disease status, disease, and KPS, were not found to significantly influence survival.

Table 3 highlights variables significantly associated with TRM and OS among the subset of 416 HCT recipients with early or intermediate AML or MDS or chemosensitive NHL transplanted between 2008 and 2013. Female relative to male recipients (HR, 1.30; 95% CI, 1.03-1.65; $P = .029$) and myeloablative conditioning as opposed to RIC/NMA (HR, 1.60; 95% CI, 1.13-2.28; $P = .009$) were associated with higher mortality. Conditioning regimen intensity was the only significant covariate associated with TRM (HR, 2.06; 95% CI, 1.32-3.22; $P = .001$) in this subset.

Supplemental Figure 1A-D demonstrates OS and TRM, respectively, for patients with AML or MDS who underwent transplantation

between 2008 and 2013 based upon both disease risk at time of transplantation (early/intermediate disease vs advanced disease) and also by comorbidity score (ie, HCT <3 vs ≥3). High comorbidity in this population appeared to have a greater adverse impact on patients with advanced or active disease at time of transplant as opposed to patients with early or intermediate disease (ie, in remission) at the time of transplant.

Discussion

In the current observational study, we report on the utilization, characterization and prognostic factors associated with allogeneic HCT in adults ≥70 years. Our findings, derived from a large national cohort of patients transplanted in the United States over the last decade, demonstrate that the absolute number and proportion of allogeneic transplants performed for adults in their eighth decade has risen steadily on a yearly basis since 2000, such that patients ≥70 years now represent nearly 4% of allogeneic HCT recipients.

Several factors spurred the increase in transplant volume for this population. The majority of growth was in fact due to increasing numbers of patients with early or intermediate-risk AML or MDS as defined by the CIBMTR (ie, AML in CR1 or greater; MDS with <5% blasts) transplanted since 2008. Greater utilization of HCT for MDS beginning after 2010 coincides with the decision in the United States to cover this disease indication for Medicare beneficiaries
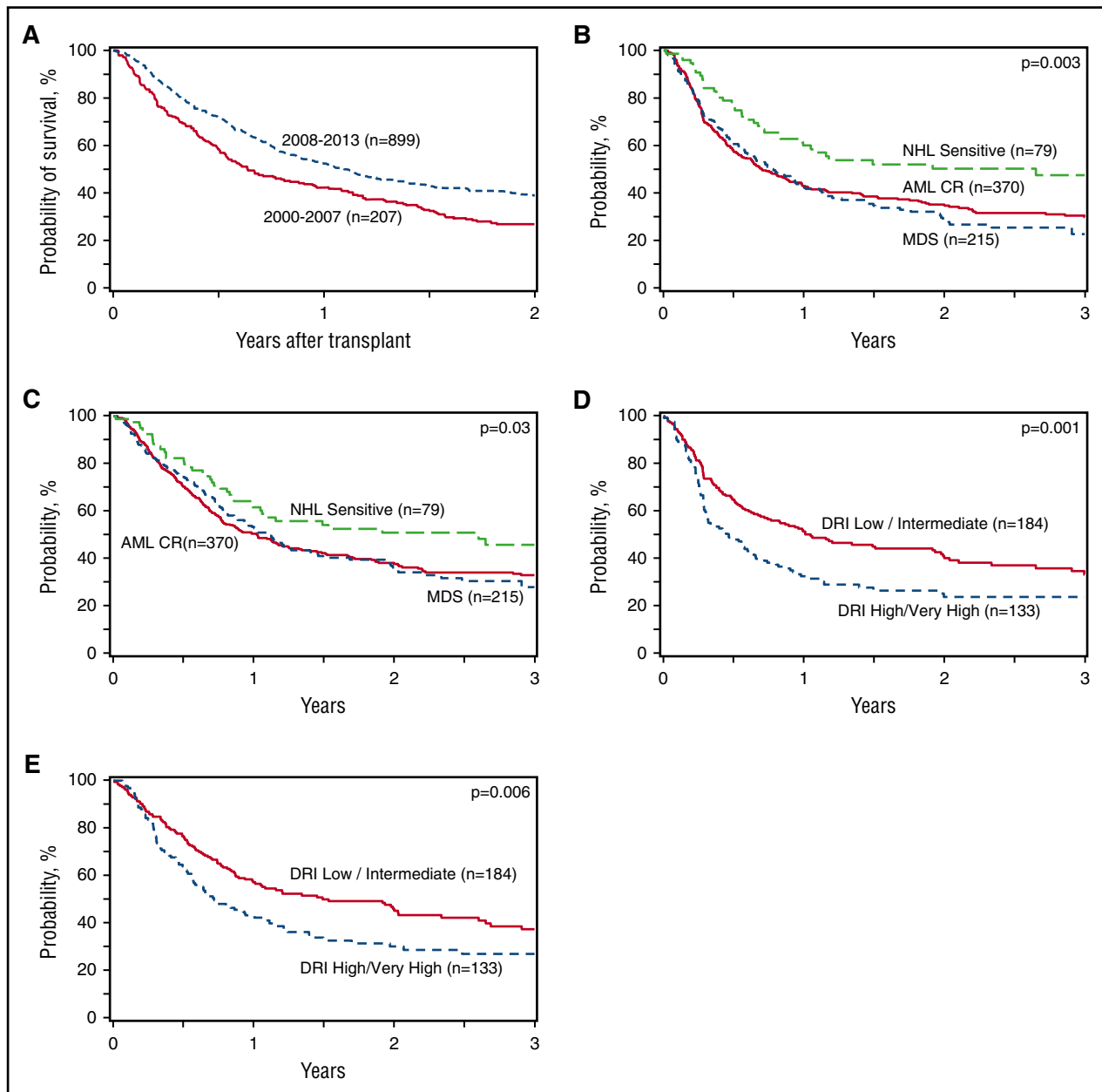
Figure 2. Allogeneic HCT outcomes in adults 70 years and older. (A) OS after HCT in patients ≥70 years by year of transplant (2000-2007 vs 2008-2013). (B) Disease-free survival after HCT in patients ≥70 years with AML in remission, myelodysplasia, and chemotherapy-sensitive NHL from 2008 to 2013. (C) OS after HCT in patients ≥70 years with AML in remission, myelodysplasia, and chemotherapy-sensitive NHL from 2008 to 2013. (D) Disease-free survival after HCT in patients ≥70 years from 2008 to 2013 according to DRI. (E) OS after HCT in patients ≥70 years from 2008 to 2013 according to DRI.

participating in an approved clinical study through the Center for Medicare and Medicaid Services Coverage with Evidence Development.[23] Additionally, the increasing use of unrelated donors (and, to some extent, haploidentical or cord blood donor stem cell sources) relative to sibling donors fueled transplant growth by substantially expanding donor availability. Perhaps the most important yet difficult to measure factor is the societal changes that have prompted physician and patient willingness to consider transplant. Similar trends in uptake for older patients have been reported in autologous transplants where donor sources are irrelevant, as well as in solid organ transplantation.[24,25]

Despite increased utilization of HCT for this older adult population, the relatively small number of allogeneic transplants confirms reports by others[26,27] that the vast majority of adults aged ≥70 years

with transplant-eligible hematologic malignancies are not undergoing HCT. For example, according to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, there are ~3000 new cases of AML diagnosed per year in adults aged 70 to 79 years in the United States (http://seer.cancer.gov/). Our data reveal that only 253 AML patients aged ≥70 years underwent allogeneic HCT between 2012 and 2013, representing only 4% of the population of newly diagnosed AML patients in their eighth decade of life. Transplant was even more rarely pursued in this age group for other disease indications, such as NHL (n = 113) and acute lymphoblastic leukemia (n = 25).

The lack of transplant outcome data in this age group has been a major impediment and previously has been restricted to reports

Table 3. Multivariate models for overall mortality (1 − OS) and TRM in patients aged 70 years and older who received an allogeneic HCT

Effect	No.	HR	95% CI	P
Overall mortality				
HCT-comorbidity index				
0-2	479	1.000	—	—
≥3	415	1.269	1.070, 1.504	.0061
Donor type				.0046*
HLA-matched, related	202	1.000	—	—
HLA-mismatched, related	67	1.209	0.848, 1.724	.2932
HLA-matched, URD < = 30 y old	233	0.933	0.726, 1.199	.5874
HLA-matched, URD > 30 y old	210	1.144	0.898, 1.457	.2754
HLA-matched, URD of unknown age	19	0.838	0.425, 1.649	.6080
HLA-mismatched, URD	67	1.324	0.945, 1.854	.1025
HLA matching unknown, URD	45	1.178	0.782, 1.775	.4340
UCB	51	1.963	1.372, 2.809	.0002
Conditioning intensity				
RIC/NMA	791	1.000	—	—
Overall mortality for patients with early/intermediate AML/MDS and chemosensitive NHL				
Sex				
Male	359	1.00	—	—
Female	165	1.30	1.03-1.65	.03
Conditioning intensity				
RIC/NMA	473	1.00	—	
MA	50	1.60	1.13-2.28	.009
TRM for patients with early/intermediate AML/MDS and chemosensitive NHL				
Conditioning intensity				
RIC/NMA	473	1.00	—	—
MA	50	2.06	1.32-3.22	.001

The first model for overall mortality in a population from 2008 to 2013 and all hematologic malignances. The second multivariate analysis includes models for overall mortality for patients with early/intermediate AML/MDS and chemosensitive NHL and TRM for a subset of patients with early and intermediate AML and MDS who received an allogenic HCT from 2008 to 2013.

MA, myeloablative; UCB, umbilical cord blood; URD, unrelated donor.

*Donor type variable was tested with 7 degrees of freedom and divided the group of matched unrelated donor according to donor age divided at the median.

including small numbers of these patients.[11,27] We found that transplant survival has significantly improved over time for this older adult population, with 2-year PFS and OS estimates of 32% (95% CI, 29% to 36%) and 39% (95% CI, 35% to 42%), respectively, for HCT recipients transplanted in the more recent era of 2008-2013. As TRM and severe acute GVHD did not change over time, improvements were likely mediated in part by transplant in patients with less advanced disease. Consistent with this, a greater proportion of patients entered transplant with earlier-risk disease (recognizing many were missing disease risk in earlier years), and improvements occurred in PFS and cumulative incidence of disease relapse.

Given the methodological issues and biases associated with retrospectively comparing treatment approaches, prospective studies are required to effectively evaluate HCT versus non-HCT therapies in older adults for each disease indication. Few studies report outcomes of patients ≥70 years after nontransplant treatment to benchmark these results, and lack of consistent patient health information reported in these studies hinders identification of transplant-eligible subsets. In a population study of AML from the Netherlands, 69% of patients ≥70 years received some form of chemotherapy, but no patients were allografted, resulting in dismal 1- and 5-year survival rates of 15% and 2%, respectively, for patients diagnosed between 2007 and 2012.[28] Thus, our study outcomes for AML patients transplanted between 2008 and 2013, revealing 2-year PFS and OS of 36% and 38%, respectively, appear extremely encouraging and suggest that select older patients achieve a substantial disease and survival benefit after HCT.

Concerns regarding treatment-related morbidity and mortality likely account for reluctance to offer transplant to older patients. Our findings that TRM has remained stable over the decade, with 2-year estimates at 30% to 35%, is similar to the findings of the registry

analysis, where 2-year TRM ranged from 25% to 39% in adults ≥40 years with AML and MDS following RIC HCT, without significant differences across age groups.[7] Registry summaries inclusive of heterogeneous disease status, donor type, and conditioning regimen may be less favorable than institutional protocol reports of more selected patients yet reflect present population-based practice patterns and results. Although supportive care for hematologic malignancy and transplant recipients has improved considerably in recent years, so much so as to allow the application of allogeneic HCT to patients ≥70 years, appreciable TRM remains a barrier to transplant utilization and success in this group. Impairments in adaptive immune response with aging are accentuated in the allogeneic transplant setting and likely contribute to the relatively high rates of transplant-related morbidity and mortality in older patients.[29] Strategies to overcome thymic impairments with aging and allogeneic transplant are of considerable interest.[30] Higher rates of TRM in those patients 70 years and older with advanced disease and high comorbidity suggest that transplant should be pursued with particularly caution in such patients.

To reduce TRM, we must consider improvements in patient selection and further refine the transplant process to allow for less toxicity and morbidity in older adults. Similar to others,[11] we found that inferior survival was associated with high comorbidity, albeit with only a modest effect (HR, 1.27; 95% CI, 1.07-1.51). Patients ≥75 years did not fare significantly worse than those 70 to 74 years of age. Therefore, age alone or moderate degrees of comorbidity are insufficient to determine transplant eligibility. Enhanced discrimination may be obtained with the use of geriatric assessment prior to HCT.[31] Geriatric assessment for evaluation and guided interventions warrant additional research to abrogate morbidity and mortality.[15,32] More precise risk stratification for TRM, if not survival, may paradoxically

expand the number of older patients eligible for transplant by delineating a larger pool of patients with acceptable transplant risks.

Similar to younger patients, disease relapse remains the primary cause of death in older transplant recipients. However, more intensive transplant conditioning via myeloablative regimens was associated with worse OS in the whole cohort and in the subset of early/intermediate AML/MDS and chemosensitive NHL. While new disease scoring systems such as the DRI- and minimal residual disease–based assessments have been used to evaluate relapse risk in younger HCT patients, the importance of these tools in older patients is less established.[21,33] For example, independent of the DRI, older patients fare worse, and minimal residual disease measures have a less pronounced effect on relapse after NMA transplant for AML and have not been shown to affect survival in this population.[33] This likely reflects the adverse biology of disease in older age in that even after adjustments for adverse disease features, older adults routinely demonstrate outcomes significantly inferior to those of younger adults.[34,35] This underscores the need to move to transplant expeditiously after initial treatment–induced response as well as to explore posttransplant maintenance and adoptive immunotherapy approaches following RIC or NMA allogeneic HCT in older adults.

In summary, the utilization of allogeneic HCT in adults aged ≥70 years with hematologic malignancies has markedly increased over the past decade. Nearly 40% of adults in this age group are alive at 2 years following transplant, suggesting that this approach is feasible, offers promising disease control, and should be considered more frequently for patients in their eighth decade with transplant-eligible diseases.

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Authorship

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1164   MUFFLY et al   BLOOD, 31 AUGUST 2017 · VOLUME 130, NUMBER 9

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Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States

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