Effect of Age on Outcome of Reduced-Intensity Hematopoietic Cell Transplantation for Older Patients With Acute Myeloid Leukemia in First Complete Remission or With Myelodysplastic Syndrome

Brian L. McClune, Daniel J. Weisdorf, Tanya L. Pedersen, Gisela Tunes da Silva, Martin S. Tallman, Jorge Sierra, John DiPersio, Armand Keating, Robert P. Gale, Biju George, Vikas Gupta, Theresa Hahn, Luis Isola, Madan Jagasia, Hillard Lazarus, David Marks, Richard Maziarz, Edmund K. Waller, Chris Bredeson, and Sergio Giralt

From the University of Minnesota Medical Center; Center for International Blood and Marrow Transplant Research, Minneapolis, MN; Northwestern University, Chicago, IL; Washington University, St Louis, MO; Celgene, Summit, NJ; Roswell Park Cancer Institute, Buffalo; Mount Sinai Medical Center, New York, NY; Vanderbilt University Medical Center, Nashville, TN; Case Western Reserve University, Cleveland, OH; Oregon Health and Science University, Portland, OR; Emory University, Atlanta, GA; Medical College of Wisconsin, Milwaukee, WI; The University of Texas M.D. Anderson Cancer Center, Houston, TX; Universidade de São Paulo, São Paulo, Brazil; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Princess Margaret Hospital, Toronto, Ontario, Canada; Christian Medical College, Tamilnadu, India; and United Bristol Healthcare National Health Service Trust, Bristol, United Kingdom.

Submitted August 6, 2009; accepted December 16, 2009; published online ahead of print at www.jco.org on March 8, 2010.

Written on behalf of the Acute Leukemia Working Committee from the Center for International Blood and Marrow Transplantation Research (CIBMTR).

The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, Department of the Navy, Department of Defense, Health Resources and Services Administration, National Marrow Donor Program, or any other agency of the US Government.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Brian L. McClune, DO, University of Minnesota, Division of Hematology, Oncology and Transplantation, University of Minnesota, MMC 480, 420 Delaware St SE, Minneapolis, MN 55455; e-mail: bmcclune@umn.edu.

© 2010 by American Society of Clinical Oncology

0732-183X/10/2811-1878/\$20.00

DOI: 10.1200/JCO.2009.25.4821

ABSTRACT

Purpose

Acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) primarily afflict older individuals. Hematopoietic cell transplantation (HCT) is generally not offered because of concerns of excess morbidity and mortality. Reduced-intensity conditioning (RIC) regimens allow increased use of allogeneic HCT for older patients. To define prognostic factors impacting long-term outcomes of RIC regimens in patients older than age 40 years with AML in first complete remission or MDS and to determine the impact of age, we analyzed data from the Center for International Blood and Marrow Transplant Research (CIBMTR).

Patients and Methods

We reviewed data reported to the CIBMTR (1995 to 2005) on 1,080 patients undergoing RIC HCT. Outcomes analyzed included neutrophil recovery, incidence of acute or chronic graft-versus-host disease (GVHD), nonrelapse mortality (NRM), relapse, disease-free survival (DFS), and overall survival (OS).

Results

Univariate analyses demonstrated no age group differences in NRM, grade 2 to 4 acute GVHD, chronic GVHD, or relapse. Patients age 40 to 54, 55 to 59, 60 to 64, and ≥ 65 years had 2-year survival rates as follows: 44% (95% CI, 37% to 52%), 50% (95% CI, 41% to 59%), 34% (95% CI, 25% to 43%), and 36% (95% CI, 24% to 49%), respectively, for patients with AML ($P = .06$); and 42% (95% CI, 35% to 49%), 35% (95% CI, 27% to 43%), 45% (95% CI, 36% to 54%), and 38% (95% CI, 25% to 51%), respectively, for patients with MDS ($P = .37$). Multivariate analysis revealed no significant impact of age on NRM, relapse, DFS, or OS (all $P > .3$). Greater HLA disparity adversely affected 2-year NRM, DFS, and OS. Unfavorable cytogenetics adversely impacted relapse, DFS, and OS. Better pre-HCT performance status predicted improved 2-year OS.

Conclusion

With these similar outcomes observed in older patients, we conclude that older age alone should not be considered a contraindication to HCT.

J Clin Oncol 28:1878-1887. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) for patients with acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) can be curative.¹ However, the increased frequency of high-risk disease phenotypes such as adverse cytogenetics and possibly higher rates of peri-transplantation mortality have limited the application of HCT in older patients.²⁻⁶ These same patients may be considered ineligible for

HCT as a result of traditional age limits or other medical comorbidities.^{7,8}

In an effort to explore graft-versus-leukemia effects without major regimen-related toxicity, many investigators have lowered the doses of radiation or alkylating agents used in the conditioning regimen.^{9,10} In single- and multi-institution analyses, nonmyeloablative (NMA) or reduced-intensity conditioning (RIC) regimens have demonstrated the feasibility and efficacy of these strategies in older patients with hematologic malignancies. However,

few reports provide sufficient clinical and disease-related detail to clarify the results of HCT in older patients,¹¹⁻¹⁶ and the limits of these data have compromised clinical decision making for older patients. In this analysis, we examine post-HCT outcomes in older (including age > 65 years) versus younger patients undergoing allografting to evaluate patient, disease, and treatment factors that may modify transplantation outcomes.

PATIENTS AND METHODS

Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR), a voluntary working group of more than 450 transplantation centers worldwide, contribute data on consecutive allogeneic HCTs to a statistical center housed both at the Medical College of Wisconsin (Milwaukee, WI) and the National Marrow Donor Program (Minneapolis, MN). Patients are observed longitudinally with yearly follow-up. Computerized checks for errors and onsite audits of participating centers ensure data quality. Physician review of data and additional requested data from reporting centers were included. Observational studies conducted by the CIBMTR are done so with a waiver of informed consent and in compliance with Health Insurance Portability and Accountability Act regulations as determined by the Institutional Review Board and the Privacy Officer of the Medical College of Wisconsin.

Patient Selection

Patients, age 40 years or older, receiving an RIC or NMA HCT for AML in first complete remission (CR1) or MDS between 1995 and 2005 from a related or unrelated donor (URD) were included in this analysis. AML could have been de novo or progressed from MDS. Patients who received prior cord blood allografts were excluded, but patients receiving prior autografts were not.

A total of 1,080 patients were identified; 545 patients had AML (age 40 to 79 years), and 535 patients had MDS (age 40 to 78 years). The patients were included from 148 centers. Patients were divided into the following four age cohorts for analysis: 40 to 54, 55 to 59, 60 to 64, and ≥ 65 years. Unfavorable-, intermediate-, or favorable-risk cytogenetics were assigned according to Slovak et al¹⁷ for AML patients. Cytogenetics for MDS (good, intermediate, or poor risk) were classified based on the International Prognostic Scoring System.¹⁸ International Prognostic Scoring System scores could not be reliably calculated as a result of some missing data elements. For analysis, MDS was classified as either early (refractory anemia, acquired idiopathic sideroblastic anemia, or pre-HCT marrow blasts < 5%) or advanced (refractory anemia excess blasts, refractory anemia excess blasts in transformation, chronic myelomonocytic leukemia, or marrow blasts $\geq 5\%$). CIBMTR classifications of URD matching were used to define well-matched, partially matched, or mismatched categories.¹⁹ Preparative regimens were classified as either RIC or NMA. RIC regimens were defined by established CIBMTR functional definitions and included any regimen consisting of the following: ≤ 5 Gy of total-body irradiation as a single fraction or ≤ 8 Gy if fractionated; less than 9 mg/kg of busulfan oral (or intravenous equivalent); less than 140 mg/m² of melphalan; less than 10 mg/kg of thiopeta; or carmustine, etoposide, cytarabine, and melphalan regimen.²⁰ All other regimens were classified as NMA according to the definition by Champlin et al²¹ where prompt hematopoietic recovery could reasonably be expected without a transplantation within 28 days, often with mixed chimerism.

Study End Points and Definitions

Primary outcomes were overall survival (OS), disease-free survival (DFS; defined as survival without death or relapse), nonrelapse (treatment-related) mortality (NRM; defined as any death in the first 28 days after transplantation or any death after day 28 in continuous remission), and hematologic relapse. All data were censored at date of last reported follow-up. Secondary end points included neutrophil recovery (defined as time to absolute neutrophil count of ≥ 500 neutrophils/mL sustained for 3 consecutive days), incidence of grade

2 to 4 acute graft-versus-host disease (GVHD), and presence or absence of chronic GVHD, as defined.^{22,23}

Statistical Analysis

Patient-, disease-, and transplantation-related variables were compared between age cohorts using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Univariate probabilities of DFS and OS were calculated using the Kaplan-Meier estimator with variance estimated by Greenwood's formula. Probabilities of neutrophil recovery, acute and chronic GVHD, NRM, and relapse were calculated using cumulative incidence curves to accommodate competing risks. Ninety-five percent CIs for all probabilities and *P* values of pairwise comparisons were derived from pointwise estimates and calculated using standard techniques.

Age groups were compared using Cox proportional hazards regression models for acute and chronic GVHD and neutrophil recovery. The proportional hazards assumption for all the variables was tested. Time-dependent covariate regression coefficients were used to model time-varying effect when the proportionality assumption did not hold. This occurred only in the modeling for neutrophil recovery. The optimal time cut point was determined by the maximum likelihood method. The proportionality assumption was further examined for the Cox model. For OS, DFS, NRM, and relapse, a forward stepwise method was used to build regression models, and analysis was performed using the pseudovalue technique.²⁴ This approach allows one to fit different models for each time point of interest without requirement for the assumption of proportional hazards. For OS and DFS, the pseudovalues were computed based on the Kaplan-Meier estimator of the survival distribution. For NRM and relapse, the pseudovalue analysis was conducted based on cumulative incidence functions because death and relapse are competing risks. Patient variables were considered in the model-building procedure, but because patient age was the main interest of this study, it was included in all steps of model building. Patient-related variables included sex and Karnofsky performance score of less than 80 versus ≥ 80 . Disease-related variables included AML CR1; AML with prior MDS versus de novo AML; early MDS versus advanced MDS; time from diagnosis to transplantation (< $\nu \geq 1$ year); and cytogenetics (favorable/intermediate ν unfavorable for AML and good/intermediate ν poor for MDS). Transplantation-related variables included donor age, donor/recipient cytomegalovirus status (negative/negative ν negative/positive ν positive/negative ν positive/positive), donor match (HLA-matched sibling ν well-matched URD ν partially matched URD ν mismatched URD), graft (bone marrow ν peripheral-blood graft), GVHD prophylaxis (cyclosporine/tacrolimus $\pm$ methotrexate $\pm$ other ν other), donor/recipient sex match (male/male ν male/female ν female/male ν female/female), and conditioning regimen intensity (RIC ν NMA). Risk factors with *P* < .05 were included in the model. The potential interaction between the main effect of age and all significant covariates were examined. All computations were performed using the statistical package SAS Version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Tables 1 and 2 list patient-, disease-, and transplantation-related variables across age groups for AML and MDS patients, respectively. Of the 545 patients with AML, 195 patients (36%) were older than 60 years of age, and 63 patients (12%) were ≥ 65 years old. The majority of patients underwent transplantation for de novo AML, but this was less common in the older age cohorts (*P* < .001). Nearly all patients had either unfavorable- or intermediate-risk cytogenetics; $\geq 40\%$ of patients in all groups had normal cytogenetics. Use of HLA-matched siblings and URD donors varied across the four groups, as did donor age. Most patients (86%) received peripheral-blood stem cells versus bone marrow (*P* < .001). The remaining variables of sex, performance status, interval from diagnosis to transplantation, donor/recipient sex

Table 1. Demographics and Clinical Characteristics of Patients With AML in First Complete Remission Age $\geq$ 40 Years Receiving Allogeneic HCT From 1995 to 2005

Characteristic	No. of Evaluable Patients	Age								P
		40-54 Years		55-59 Years		60-64 Years		≥ 65 Years		
		No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	
No. of patients	545	201		149		132		63		
No. of centers		89		62		57		38		
Age, years	545									< .001
Median		49		58		62		67		
Range		40-54		55-59		60-64		65-79		
Male	543	97	49	90	60	77	59	34	54	.11
Karnofsky performance score at transplantation ≥ 80	506	169	84	126	85	116	88	53	84	.38
Prior autologous transplantation	545	5	2	4	3	2	2	0	0	.57
AML	517									< .001
De novo AML		162	82	96	69	71	58	34	58	
Previous MDS/MPD		35	18	43	31	51	42	25	42	
Therapy-related AML	544	28	14	21	14	20	15	7	11	.89
Cytogenetic risk classification	482									.79
Favorable		8	5	0	0	3	2	0	0	
Intermediate		134	77	113	69	90	69	46	74	
Unfavorable		33	19	50	31	38	29	16	26	
Interval from diagnosis to transplantation, months	545									.21
Median		5		5		6		5		
Range		1-24		2-22		2-125		1-27		
Donor	545									.01
HLA-identical sibling		110	55	60	40	53	40	32	51	
Unrelated		91	45	89	60	79	60	31	49	
Unrelated donor/recipient HLA match	280									.49
Well matched		63	72	55	63	49	64	23	79	
Partially matched		16	18	22	25	23	30	5	17	
Mismatched		9	10	10	11	4	5	1	3	
Donor age, years	539									< .001
Median		43		43		45		54		
Range		19-65		19-72		19-74		21-78		
Donor/recipient sex match	540									.45
Male/male		59	30	62	42	46	35	20	32	
Male/female		57	29	34	23	30	23	19	30	
Female/male		38	19	28	19	31	24	14	22	
Female/female		44	22	25	17	23	18	10	16	
Donor-recipient CMV match	533									.70
Negative/negative		40	20	24	17	32	25	14	23	
Negative/positive		62	31	46	32	40	31	25	40	
Positive/positive		75	38	57	39	47	36	21	34	
Positive/negative		20	10	17	12	11	8	2	3	
Graft type	545									< .001
Bone marrow		43	21	18	12	13	10	2	3	
Peripheral blood		158	79	131	88	119	90	61	97	
Year of transplantation	545									.009
1995-2002		84	42	46	31	38	29	14	22	
2003-2005		117	58	103	69	94	71	49	78	
Conditioning intensity	545									< .001
Reduced intensity		150	75	97	65	77	58	30	48	
Nonmyeloablative		51	25	52	35	55	42	33	52	
GVHD prophylaxis	545									.001
CsA/tacrolimus + MTX, no TCD		77	38	32	21	31	23	14	22	
CsA/tacrolimus + other, no TCD		81	40	74	50	77	58	38	60	
CsA/tacrolimus + other with TCD		38	19	41	28	24	18	10	16	
TCD, no CsA/tacrolimus		2	1	1	1	0	0	0	0	
Other		3	2	1	1	0	0	1	1	
Follow-up of survivors, months	232									
Median		37		25		36		29		
Range		2-110		1-87		3-96		3-59		

Abbreviations: AML, acute myelogenous leukemia; HCT, hematopoietic cell transplantation; MDS/MPD, myelodysplastic syndrome/myeloproliferative disorder; HLA, human leukocyte antigen; CMV, cytomegalovirus; GVHD, graft-versus-host-disease; CsA, cyclosporine; MTX, methotrexate; TCD, T-cell depletion.

Reduced-Intensity HCT in Older Adults With AML and MDS

Table 2. Demographics and Clinical Characteristics of Patients With MDS Age $\geq$ 40 Years Receiving Allogeneic HCT From 1995 to 2005

Characteristic	No. of Evaluable Patients	Age								P
		40-54 Years		55-59 Years		60-64 Years		≥ 65 Years		
		No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	
No. of patients	535	208		146		126		55		
No. of centers		73		64		54		28		
Age, years	535									< .001
Median		50		57		62		67		
Range		40-54		55-59		60-64		65-78		
Male	535	119	57	108	74	83	66	39	71	.009
Karnofsky performance score at transplantation ≥ 80	500	170	87	118	87	102	87	42	81	.90
Prior autologous transplantation	535	23	11	15	10	8	6	7	13	.46
Disease status at transplantation	522									.11
Early		86	43	52	36	45	36	22	43	
Advanced*		116	57	93	64	79	64	29	57	
Therapy-related MDS	518	43	21	33	23	26	21	12	22	.98
Cytogenetic risk classification	439									.82
Good		0	0	0	0	0	0	1	2	
Intermediate		119	68	75	64	73	68	35	76	
Poor		55	32	42	36	35	32	10	22	
Interval from diagnosis to transplantation, months	534									.11
Median		8		9		10		9		
Range		1-302		1-132		2-153		1-120		
Donor	535									.17
HLA-identical sibling		90	43	56	38	53	42	15	27	
Unrelated		118	57	90	62	73	58	40	73	
Unrelated donor/recipient HLA match	297									.02
Well matched		55	54	51	57	46	69	27	69	
Partially matched		33	32	27	30	18	27	9	23	
Mismatched		14	14	11	12	3	4	3	8	
Donor age, years	527									.04
Median		41		41		47		36		
Range		20-65		21-71		19-75		20-75		
Donor-recipient sex match	534									.10
Male/male		75	36	68	47	55	44	24	44	
Male/female		49	24	22	15	30	24	11	20	
Female/male		44	21	40	27	27	22	15	27	
Female/female		40	19	16	11	13	10	5	9	
Donor-recipient CMV match	514									.36
Negative/negative		51	25	45	34	36	30	8	15	
Negative/positive		51	25	31	23	30	25	14	27	
Positive/positive		78	39	45	34	48	40	26	50	
Positive/negative		22	11	18	14	7	6	4	8	
Graft type	535									.02
Bone marrow		52	25	33	23	15	12	8	15	
Peripheral blood		156	75	113	77	111	88	47	85	
Year of transplantation										.05
1995-2002	535	103	50	62	42	52	41	16	29	
2003-2005		105	50	84	58	74	59	39	71	
Conditioning intensity	535									.07
Reduced intensity		163	78	99	68	87	69	36	65	
Nonmyeloablative		45	22	47	32	39	31	19	35	
GVHD prophylaxis	535									.07
CsA/tacrolimus + MTX, no TCD		60	29	27	18	33	26	13	24	
CsA/tacrolimus + other, no TCD		82	39	78	53	51	40	30	55	
CsA/tacrolimus + other with TCD		64	31	38	26	38	30	12	22	
TCD, no CsA/tacrolimus		0	0	0	0	1	1	0	0	
Other		2	1	3	2	3	2	0	0	
Follow-up of survivors, months	194									
Median		36		40		35		36		
Range		2-86		3-86		3-68		3-85		

Abbreviations: MDS, myelodysplastic syndrome; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; CMV, cytomegalovirus; GVHD, graft-versus-host-disease; CsA, cyclosporine; MTX, methotrexate; TCD, T-cell depletion.

*Advanced MDS includes refractory anemia excess blasts, refractory anemia excess blasts in transformation, chronic myelomonocytic leukemia, or marrow blasts $\geq$ 5%.

Table 3. Univariate Outcome Probabilities for Patients Age ≥ 40 Years Receiving Allogeneic HCT for AML in First Complete Remission

Outcome Event	Age Group												P*
	40-54 Years			55-59 Years			60-64 Years			≥ 65 Years			
	No. of Patients	Probability (%)	95% CI (%)	No. of Patients	Probability (%)	95% CI (%)	No. of Patients	Probability (%)	95% CI (%)	No. of Patients	Probability (%)	95% CI (%)	
Neutrophil engraftment at 28 days	200	89	84 to 93	149	92	87 to 96	132	92	87 to 96	63	97	91 to 100	.14
Acute GVHD at 100 days	199	33	26 to 39	149	35	27 to 43	131	35	27 to 43	63	33	22 to 45	.96
Chronic GVHD at 2 years	200	41	34 to 48	149	49	40 to 58	132	43	34 to 52	63	53	40 to 65	.30
Nonrelapse mortality	201			149			132			63			
100 days		11	7 to 16		6	3 to 10		13	8 to 20		10	4 to 18	.16
1 year		21	15 to 27		18	12 to 25		24	17 to 33		30	19 to 42	.29
2 years		25	19 to 32		22	16 to 30		32	23 to 41		34	22 to 47	.26
Relapse at 2 years	201	33	26 to 40	149	34	27 to 42	132	37	29 to 47	63	33	21 to 46	.87
Disease-free survival, years	201			149			132			63			
1		51	43 to 58		49	41 to 57		44	35 to 53		48	36 to 61	.75
2		42	35 to 49		43	35 to 52		31	22 to 40		34	22 to 47	.15
Overall survival at 2 years	201	44	37 to 52	149	50	41 to 59	132	34	25 to 43	63	36	24 to 49	.06

Abbreviations: HCT, hematopoietic cell transplantation; AML, acute myelogenous leukemia; GVHD, graft-versus-host disease.

*Pointwise *P* value.

match, donor/recipient cytomegalovirus match, and URD/recipient HLA match were well balanced in the different age groups. Conditioning regimens were primarily fludarabine based (43%; $P < .001$; data not shown) and most often RIC (48% to 75%) versus NMA ($P < .001$). GVHD prophylaxis most often included a calcineurin inhibitor with or without methotrexate. Median follow-up time for the four age cohorts ranged from 25 to 37 months.

In the MDS cohort (Table 2), 535 patients were identified; 181 patients (34%) were ≥ 60 years of age, and more males were represented. Most patients presented with intermediate- or poor-risk cytogenetics. Peripheral-blood stem cells (80%) were the most frequent graft type. Donor source varied across the age categories; 60% of all patients received an URD allograft, including 40 patients (73%) older than age 65 years. Most transplantations used a fludarabine-based

regimen (52%; $P = .001$) and RIC (65% to 78%) versus NMA for conditioning. Median follow-up time for the age cohorts ranged from 35 to 40 months.

Neutrophil Recovery/GVHD

For patients with AML, neutrophil recovery at day 28 was similar across age cohorts (Table 3). Cumulative incidence of recovery at day 28 was highest in the oldest patients. There was no significant difference in neutrophil recovery for patients with MDS across age groups (Table 4). Multivariate analysis demonstrated that older age favorably impacted recovery (relative risk [RR] = 1.41; 95% CI, 1.14 to 1.76; $P = .002$), as did use of RIC conditioning regimens (RR = 1.18; 95% CI, 1.02 to 1.35; $P = .02$). Chimerism data were not available for analysis.

Table 4. Univariate Outcome Probabilities for Patients Age ≥ 40 Years Receiving Allogeneic HCT for MDS

Outcome Event	Age Group												P*
	40-54 Years			55-59 Years			60-64 Years			≥ 65 Years			
	No. of Patients	Probability (%)	95% CI (%)	No. of Patients	Probability (%)	95% CI (%)	No. of Patients	Probability (%)	95% CI (%)	No. of Patients	Probability (%)	95% CI (%)	
Neutrophil engraftment at 28 days	207	83	77 to 88	146	80	73 to 86	126	88	82 to 93	55	87	77 to 95	.25
Acute GVHD at 100 days	208	33	26 to 39	145	36	28 to 44	125	31	23 to 40	55	34	22 to 47	.89
Chronic GVHD at 2 years	206	37	30 to 44	145	38	30 to 47	126	40	31 to 49	55	45	31 to 59	.79
Nonrelapse mortality	205			144			126			55			
100 days		17	12 to 22		17	12 to 24		13	8 to 20		19	10 to 30	.75
1 year		29	23 to 36		32	25 to 40		32	24 to 40		35	22 to 48	.85
2 years		33	27 to 40		39	31 to 47		35	27 to 44		39	26 to 53	.74
Relapse at 2 years	205	28	22 to 34	144	29	22 to 37	126	29	21 to 38	55	25	14 to 38	.95
Disease-free survival, years	205			144			126			55			
1		44	37 to 51		40	32 to 49		43	34 to 52		42	29 to 56	.91
2		39	32 to 46		32	24 to 40		35	27 to 45		36	23 to 49	.68
Overall survival at 2 years	208	42	35 to 49	146	35	27 to 43	126	45	36 to 54	55	38	25 to 51	.37

Abbreviations: HCT, hematopoietic cell transplantation; MDS, myelodysplastic syndrome; GVHD, graft-versus-host disease.

*Pointwise *P* value.

At day 100, the incidence of grade 2 to 4 acute GVHD was similar across all groups for both diseases (AML: 33% to 35%, $P = .96$; MDS: 31% to 36%, $P = .89$). Age had no significant effect on the incidence of acute GVHD. Multivariate analysis showed a higher risk of acute GVHD when using a well-matched URD (RR = 1.67; 95% CI, 1.32 to 2.12; $P < .001$) or partially matched URD (RR = 1.94; 95% CI, 1.44 to 2.62; $P < .001$) compared with an HLA-identical sibling donor. Multivariate analysis showed that age was associated with a borderline higher risk of chronic GVHD, although only in the oldest age cohort (RR = 1.39; 95% CI, 1.01 to 1.91; $P = .05$).

NRM

Cumulative incidences of NRM did not differ between the age cohorts either at day 100 (6% to 13%; $P = .16$) or 1 year (18% to 30%; $P = .29$) for AML (Table 3). In patients with AML, NRM at 1 year was 30% for patients ≥ 65 years of age compared with 21% for patients between 40 and 54 years old. In patients with MDS, NRM at 1 year was 29% for the youngest cohort compared with 35% for the oldest cohort (Table 4). In combined multivariate analysis for both diseases, lower KPS, worsening HLA disparity, MDS (whether cytogenetically good, intermediate, or poor risk), unfavorable-risk AML, and increasing donor age each adversely affected 1-year NRM, whereas use of an NMA conditioning regimen was associated with a borderline lower risk (odds ratio [OR] = 0.75; 95% CI, 0.57 to 1.0; $P = .05$). At 2 years, only HLA disparity, cytogenetic risk group, and increasing donor age retained prognostic significance. Recipient age did not significantly impact NRM (Fig 1A). The most common primary causes of death in both the AML and MDS groups were relapse (33%), infection (21%), GVHD (14%), and organ failure (14%).

Relapse

Relapse rates at 2 years were similar across age groups for both AML ($P = .87$) and MDS ($P = .95$). In patients with early MDS, 2-year

relapse rates ranged from a low of 15% (95% CI, 4% to 31%) in the oldest age group to a high of 27% (95% CI, 16% to 40%) in patients age 55 to 59 years ($P = .57$). Relapse rates in patients with advanced MDS were slightly higher (30% to 35%) overall, but again showed no differences between the age groups ($P = .95$). Combined multivariate analysis demonstrated significantly more relapse at 2 years in patients receiving NMA conditioning regimens (OR = 1.46; 95% CI, 1.15 to 1.85; $P = .002$) and in patients with unfavorable-/poor-risk cytogenetics in both AML and MDS (OR = 2.01; 95% CI, 1.42 to 2.85; $P < .001$; and OR = 1.57; 95% CI, 1.04 to 2.35; $P < .03$, respectively). Early MDS was associated with less disease relapse at 2 years (OR = 0.43; 95% CI, 0.26 to 0.71; $P < .001$). Age had no significant impact on relapse (Fig 1B).

DFS and OS

In univariate analysis, DFS at 2 years for patients with AML ($P = .15$) and MDS ($P = .68$) was similar across all age cohorts. Multivariate analysis (Table 5) showed worse DFS with older donor age, greater HLA disparity, and unfavorable-/poor-risk cytogenetics in both disease groups but confirmed no effect of recipient age ($P = .81$).

Two-year survival for patients with AML and MDS showed only modest differences across the four age groups (AML: 34% to 50%, $P = .06$; MDS: 35% to 45%, $P = .37$). In multivariate analysis (Table 5), age had no significant effect on OS ($P = .74$). However, KPS less than 80, mismatched URD, and unfavorable-risk cytogenetics all negatively impacted OS at 2 years. Kaplan-Meier estimates of DFS and OS are shown in Figure 2.

DISCUSSION

Data from the CIBMTR and the European Group for Blood and Marrow Transplantation have shown a dramatic increase in the number of allografts that are being performed using RIC regimens for a

Fig 1. Cumulative incidence of (A) nonrelapse mortality ($P = .66$) and (B) relapse ($P = .87$) in patients undergoing reduced-intensity conditioning or nonmyeloablative transplantation for acute myelogenous leukemia in first complete remission or for myelodysplastic syndrome.

Table 5. Multivariate Analysis of 2-Year Disease-Free Survival and Overall Survival After Allogeneic HCT for Patients With AML in First Complete Remission and MDS

Variable	Disease-Free Survival				Overall Survival			
	No. of Patients	OR	95% CI	P	No. of Patients	OR	95% CI	P
Age, years								
40-54	399	1.00*		.81†‡	401	1.00*		.74†‡
55-59	289	1.03	0.82 to 1.29	.81	291	1.02	0.82 to 1.27	.85
60-64	255	1.12	0.89 to 1.42	.33	255	1.09	0.86 to 1.37	.48
≥ 65	116	1.07	0.79 to 1.45	.68	116	1.16	0.86 to 1.57	.32
Significant covariates								
KPS								
≥ 80	878	1.00*		.003†§	882	1.00*		.003†§
< 80	107	1.06	0.74 to 1.51	.75	107	1.63	1.21 to 2.20	.001
Unknown	74	1.58	1.01 to 2.45	.04	74	0.87	0.61 to 1.25	.46
Donor/recipient match								
HLA-identical sibling	457	1.00*		.003†	460	1.00*		.05†
Well matched	365	1.48	1.12 to 1.95	.01	366	1.20	0.98 to 1.47	.08
Partially matched	151	1.46	1.06 to 2.02	.02	151	1.21	0.92 to 1.57	.17
Mismatched	54	2.53	1.54 to 4.15	< .001	54	1.85	1.21 to 2.85	.005
Unknown	32	1.37	0.81 to 2.31	.24	33	1.15	0.69 to 1.90	.60
Donor age (continuous)	1066	1.01	1.00 to 1.02	.02	1066	—	—	—
Cytogenetic risk group								
AML, favorable/intermediate	390	1.00*		.006†¶	390	1.00*		.006†¶
AML, unfavorable	83	2.13	1.44 to 3.14	< .001	83	2.01	1.39 to 2.91	< .001
AML, unknown	63	1.01	0.68 to 1.49	.97	63	0.89	0.60 to 1.32	.57
MDS, good/intermediate	204	1.12	0.88 to 1.42	.37	206	1.04	0.81 to 1.33	.75
MDS, poor	228	1.27	1.01 to 1.61	.05	229	1.22	0.96 to 1.54	.10
MDS, unknown	91	1.15	0.82 to 1.61	.42	92	1.09	0.78 to 1.51	.62

Abbreviations: HCT, hematopoietic cell transplantation; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; KPS, Karnofsky performance score.

*Reference group.

†Overall P value.

‡ χ^2 test with 3 df.§ χ^2 test with 2 df.|| χ^2 test with 4 df.¶ χ^2 test with 5 df.

variety of hematologic conditions.^{25,26} The advent of RIC has allowed for increased use of allografting in older and less fit patients.^{27,28} Although the median age of the patients undergoing HCT has increased, the proportion of patients older than age 60 years, and particularly older than age 65 years, remains relatively small.²⁹ This analysis from the CIBMTR is one of the largest series of older patients with AML or MDS treated with allogeneic HCT, yet still the population of patients older than age 65 years is only 12% of the AML cohort and 10% of the MDS cohort over a 10-year period as a result of uncertainty regarding outcomes in the older patient and hesitance of providers for referral to transplantation centers.

We observed that transplantation toxicity, relapse, and survival for older adults are not significantly different than those for younger adults undergoing a similar NMA or RIC allogeneic HCT. Previous nontransplantation studies have shown uniformly poor survival in patients older than age 60 years, with little improvement over the last 30 years.^{4,30} Our data indicate that allogeneic HCT offers a treatment option able to provide long-term disease control in almost one third of patients older than age 40 years, which was similar even in the oldest cohort of patients ≥ 65 years old.

HCT for these older patients did not result in excess NRM, as many clinicians might fear. NRM was similar across all four age co-

horts, ranging from 18% to 35% at 1 year. The incidence of acute and chronic GVHD was also similar across all age cohorts, although a trend toward more chronic GVHD was noted in the oldest age population in which more URDs were used. This is not surprising because use of URD is often reported to be associated with a higher risk of chronic GVHD.^{31,32} We recognize that small patient numbers may confound recognition of small differences in outcomes; however, these encouraging data help confirm the overall safety and tolerability of the procedure, even in the oldest group.

Older age was not associated with higher relapse rates despite the high-risk disease represented in this population. However, regimen intensity may still be important because NMA regimens were associated with higher relapse rates. Other series have shown that greater regimen intensity leads to less relapse, although possibly at the expense of higher NRM.³³⁻³⁵ Analysis of the various RIC regimens used for transplantation was beyond the scope of this article. No formal comparison with published series of patients undergoing myeloablative transplantation was made because most exclude patients older than age 60 years and this would confound the analysis of age and its impact. Because the best preparative regimen for allogeneic HCT is still uncertain, carefully designed prospective trials are essential to determine the contribution of a specific conditioning regimen to successful disease control.

Fig 2. Kaplan-Meier estimates for disease-free survival (DFS) in (A) patients with acute myelogenous leukemia (AML) in first complete remission (CR1) and (B) patients with myelodysplastic syndrome (MDS). Kaplan-Meier estimates for overall survival (OS) in (C) patients with AML in CR1 and (D) patients with MDS. Multivariate analysis for DFS ($P = .81$) and OS ($P = .74$) is shown in Table 5.

In this large series, OS and DFS were not significantly worse in the older patient groups. Donor age did show an association with worse DFS; however, because sibling donors are generally similar in age to their recipients, whereas URDs are often younger, analysis of this variable is confounded by donor type and HLA matching, so no further analysis was appropriate. The older patients undergoing transplantation were judged by their physicians to be fit for the rigors and risks of allotransplantation. The somewhat younger group assigned to receive NMA or RIC conditioning may have had comorbidities, making this choice clinically appropriate, but such details were not available for this analysis. Efforts to adjust for potential bias were performed using performance status at time of transplantation, and no age-associated differences were noted. It is evident from this and other studies^{36,37} that transplantation physicians can identify patients older than age 40 years who are able to undergo this procedure with reasonable safety using KPS, perhaps augmented with other comorbidity indices.

Although we are encouraged by our observations that older patients shared similar risks of NRM, relapse, and GVHD as their younger counterparts, much work remains. Novel therapies such as

monoclonal antibodies, FLT3 kinase inhibitors, and vaccination studies using leukemia antigens and dendritic cells may further complement or replace current treatments, allowing more individually targeted approaches for remission induction.³⁸⁻⁴⁰ This may increase the number of patients achieving complete remission using less toxic therapies and increase the number of candidates for allogeneic HCT. Additionally, quality-of-life studies in older individuals will become important as more patients use transplantation options as a form of therapy.

In this study, HCT resulted in 2-year survival rates of greater than 30% in all age groups, whereas conventional chemotherapy offers almost no chance of extended survival for older patients with AML or MDS. As recently reported, only a minority of patients with AML or MDS achieving complete remission after induction chemotherapy are able to undergo HCT in CR1.²⁹ Our data support active consideration of HCT in older patients. We recommend and encourage referral to a transplantation center for all potential candidate patients. We also advocate expanded insurance coverage for MDS transplantation and suggest the continued enrollment of older patients onto prospective trials of allogeneic HCT designed to test improvements in

the safety and efficacy of allografting for these older patients, who need it the most.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Armand Keating, Leukemia Lymphoma Society (U) **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** John DiPersio, Genzyme **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

REFERENCES

- Socié G, Stone JV, Wingard JR, et al: Long-term survival and late deaths after allogeneic bone marrow transplantation: Late Effects Working Committee of the International Bone Marrow Transplant Registry. *N Engl J Med* 341:14-21, 1999
- Leith CP, Kopecky KJ, Chen IM, et al: Frequency and clinical significance of the expression of the multidrug resistance proteins MDR1/P-glycoprotein, MRP1, and LRP in acute myeloid leukemia: A Southwest Oncology Group Study. *Blood* 94:1086-1099, 1999
- Leith CP, Kopecky KJ, Godwin J, et al: Acute myeloid leukemia in the elderly: Assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biologic subgroups with remarkably distinct responses to standard chemotherapy: A Southwest Oncology Group study. *Blood* 89:3323-3329, 1997
- Appelbaum FR, Gundacker H, Head DR, et al: Age and acute myeloid leukemia. *Blood* 107:3481-3485, 2006
- Grimwade D, Walker H, Harrison G, et al: The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): Analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. *Blood* 98:1312-1320, 2001
- Schoch C, Kern W, Schnittger S, et al: The influence of age on prognosis of de novo acute myeloid leukemia differs according to cytogenetic subgroups. *Haematologica* 89:1082-1090, 2004
- Finke J, Nagler A: Viewpoint: What is the role of allogeneic hematopoietic cell transplantation in the era of reduced-intensity conditioning—Is there still an upper age limit? A focus on myeloid neoplasia. *Leukemia* 21:1357-1362, 2007
- Alamo J, Shahjahan M, Lazarus HM, et al: Comorbidity indices in hematopoietic stem cell transplantation: A new report card. *Bone Marrow Transplant* 36:475-479, 2005
- Giralt S, Estey E, Albitar M, et al: Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: Harnessing graft-versus-leukemia without myeloablative therapy. *Blood* 89:4531-4536, 1997
- McSweeney PA, Niederwieser D, Shizuru JA, et al: Hematopoietic cell transplantation in older patients with hematologic malignancies: Replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood* 97:3390-3400, 2001
- Alyea EP, Kim HT, Ho V, et al: Comparative outcome of nonmyeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age. *Blood* 105:1810-1814, 2005
- Aoudjane M, Labopin M, Gorin NC, et al: Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: A retrospective survey from the Acute Leukemia Working Party (ALWP) of the European Group for Blood and Marrow Transplantation (EBMT). *Leukemia* 19:2304-2312, 2005
- Martino R, Iacobelli S, Brand R, et al: Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. *Blood* 108:836-846, 2006
- Shimoni A, Kroger N, Zabelina T, et al: Hematopoietic stem-cell transplantation from unrelated donors in elderly patients (age > 55 years) with hematologic malignancies: Older age is no longer a contraindication when using reduced intensity conditioning. *Leukemia* 19:7-12, 2005
- Bertz H, Potthoff K, Finke J: Allogeneic stem-cell transplantation from related and unrelated donors in older patients with myeloid leukemia. *J Clin Oncol* 21:1480-1484, 2003
- Gupta V, Daly A, Lipton JH, et al: Nonmyeloablative stem cell transplantation for myelodysplastic syndrome or acute myeloid leukemia in patients 60 years or older. *Biol Blood Marrow Transplant* 11:764-772, 2005
- Slovak ML, Kopecky KJ, Cassileth PA, et al: Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: A Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood* 96:4075-4083, 2000
- Greenberg P, Cox C, LeBeau MM, et al: International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 89:2079-2088, 1997
- Weisdorf D, Spellman S, Haagenson M, et al: Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: Revised definitions to predict survival. *Biol Blood Marrow Transplant* 14:748-758, 2008
- Giralt S, Ballen K, Rizzo D, et al: Reduced-intensity conditioning regimen workshop: Defining the dose spectrum—Report of a workshop convened by the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant* 15:367-369, 2009
- Champlin R, Khouri I, Shimoni A, et al: Harnessing graft-versus-malignancy: Non-myeloablative preparative regimens for allogeneic hematopoietic transplantation, an evolving strategy for adoptive immunotherapy. *Br J Haematol* 111:18-29, 2000
- Przepiorka D, Weisdorf D, Martin P, et al: 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant* 15:825-828, 1995
- Filipovich AH, Weisdorf D, Pavletic S, et al: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant* 11:945-956, 2005
- Andersen P, Klein J, Rosthøj S: Generalised linear models for correlated pseudo-observations, with applications to multi-state models. *Biometrika* 90:15-27, 2003
- Gratwohl A, Baldomero H, Frauendorfer K, et al: EBMT activity survey 2004 and changes in disease indication over the past 15 years. *Bone Marrow Transplant* 37:1069-1085, 2006
- Antin JH: Stem cell transplantation-harnessing of graft-versus-malignancy. *Curr Opin Hematol* 10:440-444, 2003
- Hegenbart U, Niederwieser D, Sandmaier BM, et al: Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. *J Clin Oncol* 24:444-453, 2006

AUTHOR CONTRIBUTIONS

Conception and design: Brian L. McClune, Daniel J. Weisdorf, Sergio Giralt

Provision of study materials or patients: Brian L. McClune, Jorge Sierra, Biju George, Vikas Gupta, Luis Isola, Madan Jagasia, Hillard Lazarus, Richard Maziarz, Edmund K. Waller, Chris Bredeson, Sergio Giralt

Collection and assembly of data: Daniel J. Weisdorf, Tanya L. Pedersen

Data analysis and interpretation: Brian L. McClune, Daniel J. Weisdorf, Tanya L. Pedersen, Gisela Tunes de Silva, Martin S. Tallman, Jorge Sierra, John DiPersio, Armand Keating, Biju George, Vikas Gupta, Theresa Hahn, Luis Isola, Madan Jagasia, Hillard Lazarus, David Marks, Richard Maziarz, Edmund K. Waller, Chris Bredeson, Sergio Giralt

Manuscript writing: Brian L. McClune, Daniel J. Weisdorf, Tanya L. Pedersen, Sergio Giralt

Final approval of manuscript: Brian L. McClune, Daniel J. Weisdorf, Tanya L. Pedersen, Martin S. Tallman, Jorge Sierra, John DiPersio, Armand Keating, Robert P. Gale, Biju George, Vikas Gupta, Theresa Hahn, Luis Isola, Madan Jagasia, Hillard Lazarus, David Marks, Richard Maziarz, Edmund K. Waller, Chris Bredeson, Sergio Giralt

28. Corradini P, Zallio F, Mariotti J, et al: Effect of age and previous autologous transplantation on non-relapse mortality and survival in patients treated with reduced-intensity conditioning and allografting for advanced hematologic malignancies. *J Clin Oncol* 23:6690-6698, 2005
29. Estey E, de Lima M, Tibes R, et al: Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). *Blood* 109:1395-1400, 2007
30. Estey E, Dohner H: Acute myeloid leukaemia. *Lancet* 368:1894-1907, 2006
31. Huisman C, Meijer E, Petersen EJ, et al: Hematopoietic stem cell transplantation after reduced intensity conditioning in acute myelogenous leukemia patients older than 40 years. *Biol Blood Marrow Transplant* 14:181-186, 2008
32. Eapen M, Logan BR, Confer DL, et al: Peripheral blood grafts from unrelated donors are associated with increased acute and chronic graft-versus-host disease without improved survival. *Biol Blood Marrow Transplant* 13:1461-1468, 2007
33. Hows JM, Passweg JR, Tichelli A, et al: Comparison of long-term outcomes after allogeneic hematopoietic stem cell transplantation from matched sibling and unrelated donors. *Bone Marrow Transplant* 38:799-805, 2006
34. Banna GL, Aversa S, Sileni VC, et al: Nonmyeloablative allogeneic stem cell transplantation (NST) after truly nonmyeloablative and reduced intensity conditioning regimens. *Crit Rev Oncol Hematol* 51:171-189, 2004
35. de Lima M, Anagnostopoulos A, Munsell M, et al: Nonablative versus reduced-intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: Dose is relevant for long-term disease control after allogeneic hematopoietic stem cell transplantation. *Blood* 104:865-872, 2004
36. Kahl C, Storer BE, Sandmaier BM, et al: Relapse risk in patients with malignant diseases given allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. *Blood* 110:2744-2748, 2007
37. Sorror M, Storer B, Sandmaier BM, et al: Hematopoietic cell transplantation-comorbidity index and Karnofsky performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. *Cancer* 112:1992-2001, 2008
38. Raza A, Jurcic JG, Roboz GJ, et al: Complete remissions observed in acute myeloid leukemia following prolonged exposure to SGN-33 (lintuzumab), a humanized monoclonal antibody targeting CD33. *Blood* 110:159, 2007 (abstr)
39. Knapper S, Burnett AK, Littlewood T, et al: A phase 2 trial of the FLT3 inhibitor lestaurtinib (CEP701) as first-line treatment for older patients with acute myeloid leukemia not considered fit for intensive chemotherapy. *Blood* 108:3262-3270, 2006
40. Rezvani K, Yong AS, Mielke S, et al: Leukemia-associated antigen-specific T-cell responses following combined PR1 and WT1 peptide vaccination in patients with myeloid malignancies. *Blood* 111:236-242, 2008

Let JOP Online Work for You

Access all content from the first to the current issue of the *Journal of Oncology Practice (JOP)*; consult ASCO Clinical Guideline summaries; link to citations from 1,100+ HighWire-hosted journals. Receive regular e-mail alerts.

Receive RSS feeds of the most-read articles from the current issue and the last two issues.

Get the latest cancer policy news. Access practice resources and tools for enhancing quality of care. Find a job through the online career center. Download content to your PDA.

Download figures into preformatted PowerPoint slides.

Visit jop.ascopubs.org to see what JOP online has to offer.

American Society of Clinical Oncology