VOLUME 33 · NUMBER 28 · OCTOBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Outcomes of Nonmyeloablative HLA-Haploidentical Blood or Marrow Transplantation With High-Dose Post-Transplantation Cyclophosphamide in Older Adults

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Published online ahead of print at www.jco.org on August 10, 2015.

Supported by National Institutes of Health Grants No. P01 CA015396 (R.J.J.) and P30 CA006973.

Presented in part at the 55th American Society of Hematology Annual Meeting, New Orleans, LA, December 7-10, 2013.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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0732-183X/15/3328w-3152w/$20.00

DOI: 10.1200/JCO.2014.60.4777

ABSTRACT

Purpose
Recent advances in nonmyeloablative (NMA), related HLA-haploidentical blood or marrow transplantation (haplo-BMT) have expanded the donor pool. This study evaluated the effect of age on NMA haplo-BMT outcomes in patients age 50 to 75 years.

Patients and Methods
A retrospective analysis was performed of 271 consecutive patients with hematologic malignancies, age 50 to 75 years, who received NMA, T-cell–replete haplo-BMT with high-dose post-transplantation cyclophosphamide.

Results
The median age was 61 years, with 115 patients (42%) age 50 to 59, 129 (48%) age 60 to 69, and 27 (10%) age 70 to 75 years. Overall, 84% of patients had intermediate- or high-/very high–risk disease. The 6-month probabilities of grade 3 or 4 acute graft-versus-host disease (GVHD) and nonrelapse mortality (NRM) were 3% and 8%, respectively. Patients in their 50s, 60s, and 70s had 6-month NRM probabilities of 8%, 9%, and 7%, respectively ($P = .20$). With a median follow-up of 4 years, corresponding 3-year progression-free survival probabilities were 39%, 35%, and 33% ($P = .65$), and corresponding 3-year overall survival probabilities were 48%, 45%, and 44% ($P = .66$). Three-year progression-free survival probabilities were 40% in acute myeloid leukemia (n = 65), 39% in aggressive non-Hodgkin lymphoma (n = 83), and 37% in indolent or mantle-cell lymphoma (n = 65). Older patient age was associated with a significantly higher risk of grade 2 to 4 acute GVHD but not grade 3 to 4 acute or chronic GVHD. No statistically significant associations were found between older age (relative to age 50 to 59 years or as a continuous variable) and NRM, relapse, or survival.

Conclusion
NMA haplo-BMT with post-transplantation cyclophosphamide has encouraging safety and survival outcomes in patients age 50 to 75 years. In patients otherwise fit for BMT, the results support consideration of this approach despite advanced age.

J Clin Oncol 33:3152-3161. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Although allogeneic blood or marrow transplantation (BMT) is the only potentially curative approach for many patients with hematologic malignancies, the inability to identify a matched donor and the sometimes prohibitive delays with matched unrelated donor BMT[1] have historically been major barriers. In contrast, partially HLA-mismatched related, or HLA-haploidentical, donors can be promptly identified for most patients. HLA-mismatched allografting used to be associated with excess risks of graft-versus-host disease (GVHD), graft failure, and nonrelapse mortality (NRM).[2-7] However, modern approaches to GVHD prophylaxis, such as high-dose post-transplantation cyclophosphamide (PTCy), have greatly reduced the morbidity of HLA-haploidentical BMT (haplo-BMT), making it a viable alternative for patients lacking HLA-matched donors.[8,9]

As a pharmacologic form of tolerance induction,[10] high-dose PTCy moderates GVHD and graft

failure as a result of the heightened chemotherapy sensitivity of proliferating, alloreactive T cells compared with nonalloreactive resting and memory T cells.[9,11] High-dose PTCy reduces GVHD (particularly grade 3 or 4 acute and chronic GVHD) and graft failure after T-cell–replete haploidentical allografting.[12-16] Moreover, greater HLA disparity does not seem to be detrimental to overall outcomes in nonmyeloablative (NMA) haplo-BMT using PTCy.[17]

Although considered experimental in many centers, the use of NMA or reduced-intensity conditioned (RIC) haplo-BMT is growing as a result of its feasibility and safety. However, there is a paucity of data on the safety and efficacy of haplo-BMT in older patients, who are disproportionally affected by hematologic malignancies.[18,19] Further, the incidence of hematologic malignancies in older patients seems to be increasing.[20] Here, we evaluated the effect of age on toxicity and survival outcomes after NMA haplo-BMT with high-dose PTCy, among patients age 50 to 75 years.

PATIENTS AND METHODS

Patients and Treatments

We retrospectively evaluated 271 consecutive patients with hematologic malignancies, age 50 to 75 years, who received NMA haplo-BMT with high-dose PTCy at Johns Hopkins (Baltimore, MD) from January 2003 through June 2013. The study received institutional review board approval, and all participants gave signed informed consent for BMT. Transplantations were performed on prospective clinical trials (228 patients; 84%) or similarly off study, with reasons for off-study treatment including insurance limitations, completed protocol accrual, and rarely ineligibility. Forty-seven percent of patients were included in previous publications.[14,17] As a result of disease biology, allografting was prioritized over autografting for transformed lymphoma, de novo diffuse large B-cell lymphoma that relapsed less than 1 year after first-line therapy[21] or was chemotherapy-refractory, and T-cell lymphoma. Eligibility criteria for NMA BMT typically included Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, left ventricular ejection fraction $\geq 35\%$, forced expiratory volume in 1 second and forced vital capacity $\geq 40\%$ predicted ($\geq 60\%$ predicted after thoracic or mantle irradiation), and absence of uncontrolled infection. Morphologic complete remission for acute leukemia[22] and at least partial remission for aggressive lymphoma[23] were standardly required.

Donors were first-degree relatives or half-siblings who shared one HLA haplotype and were mismatched at $\geq$ one locus of the unshared haplotype based on high-resolution typing at HLA-A, -B, -Cw, -DRB1, and -DQB1. Donor selection criteria included, in order of priority, medical fitness, antidonor HLA antibody status, major ABO compatibility, matched cytomegalovirus (CMV) immunoglobulin G serostatus, overall ABO compatibility, and sex (male donor preferred for male patient).

All patients received cyclophosphamide (14.5 mg/kg per day intravenously [IV] on days -6 and -5), fludarabine (30 mg/m^2 per day IV on days -6 to -2, adjusted for renal function), total-body irradiation (2 Gy on day -1), and T-cell–replete allografting (on day 0) as previously described.[14] Fludarabine was dosed using actual weight, and pre- and post-transplantation cyclophosphamide was standardly dosed using the lesser of ideal and actual weight. All but one patient received a bone marrow graft. The median infused CD34$^+$ cell dose was 4.1×10^6/kg (interquartile range, 3.2 to 5.2×10^6/kg). GVHD prophylaxis consisted of high-dose PTCy (50 mg/kg per day IV on days 3 and 4) with mesna, mycophenolate mofetil (days 5 through 35), and tacrolimus.[14] In the absence of GVHD or graft failure, tacrolimus was planned from days 5 through 180 (224 patients; 83%), per our institutional standard, or days 5 through 90 (47 patients; 17%) on a clinical trial of reduced immunosuppression. Tacrolimus was dosed with a target trough of 5 to 15 ng/mL and discontinued without taper. Filgrastim was administered from day 5 until neutrophil recovery to $\geq$ 1,000/μL. Recipients of other allogeneic transplantation regimens and those undergoing second allogeneic transplantations were excluded. Recipients of consolidative or maintenance therapy (eg, tyrosine kinase inhibitors) were included, with post-transplantation rituximab given for potential relapse reduction in 54 (42%) of 128 relevant patient cases.

Supportive care included a quinolone and *Candida albicans* prophylaxis from day 0 to neutrophil recovery and longer-term prophylaxis against *Pneumocystis jirovecii* and varicella-zoster virus. CMV-seronegative patients received transfusions from CMV-seronegative donors or leukoreduced products. CMV quantitative polymerase chain reaction was monitored weekly through at least day 60, and CMV reactivation was pre-emptively treated.

Nearly all transplantations (97%) were initiated in the outpatient setting, with hospitalization as necessary (commonly for febrile neutropenia during the night). Patients were observed until at least day 60 before discharge to the primary oncologist, standardly returning to Johns Hopkins at 6 months, 1 year, and then yearly after transplantation.

Definitions

Pretransplantation risk factors were scored using the hematopoietic cell transplantation–specific comorbidity index (HCT-CI)[24] and the three-group refined Disease Risk Index (DRI)[25] (low risk, intermediate risk, and high/very high risk), as published. ECOG PS, if not prespecified, was retrospectively evaluated at approximately day 180 and approximately day 365 for descriptive purposes, with censoring for relapse. Johns Hopkins hospitalization data are reported from the start of conditioning to day 60. Count recovery was defined by Center for International Blood and Marrow Transplant Research criteria.[26] Graft failure was defined as persistent absence, or achievement then loss, of $\geq$ 5% donor chimerism by approximately day 60 without detected bone marrow malignancy. Acute GVHD was graded by Keystone criteria.[27] Chronic GVHD was diagnosed by National Institutes of Health consensus criteria.[28]

Statistical Methods

The primary objective was to evaluate survival outcomes relative to age at BMT in patients age $\geq$ 50 years. Primary analyses evaluated age as a categorical variable (age grouped by decade or age 50 to 59 *v* $\geq$ 60 years), and secondary analyses evaluated age as a continuous variable. Group characteristics were compared with Kruskal-Wallis tests for continuous outcomes or Fisher's exact tests for categorical outcomes. Event-time distributions were measured from the date of BMT. Progression-free survival (PFS), disease-free survival, and overall survival (OS) were estimated using the Kaplan-Meier method and compared between groups with stratified log-rank statistics or Cox proportional hazard models, with stratification by BMT year (2003 to 2009 *v* 2010 to 2013). For PFS, failure was defined as relapse, progression, unplanned treatment of disease persistence, or death. For disease-free survival, failure was defined as disease persistence or death. Cumulative incidences (CuIs) of relapse/progression, NRM, GVHD, and count recovery were calculated or compared using Gray's k-sample tests or Fine and Gray's methods for competing risks.[29,30] PFS failures other than NRM were competing risks for NRM and vice versa; death was a competing risk for count recovery; and PFS failures and graft failure were competing risks for GVHD. All regression models for time-to-event end points were likewise stratified by BMT year.[31] Regression models were also adjusted for refined DRI group where specified. A hazard ratio > 1 indicates the increase in risk of having the event relative to the reference category. Significance was based on $P \leq .05$. All P values are two-sided and unadjusted for multiple comparisons. The database was locked on September 2, 2014, and analyzed using R, version 3.0.2.[32]

RESULTS

Patients and Overall Outcomes

Patient and transplantation characteristics are listed in Table 1. In this cohort of 271 patients (median age, 61 years; range, 50 to 75 years), 115 patients (42%) were age 50 to 59 years at BMT, 129 (48%) were age 60 to 69 years, and 27 (10%) were age 70 to 75 years. Fifty-three percent of patients were five out of 10 HLA antigen matched, 71% were mismatched at all three class I loci, 74% were mismatched at both

Table 1. Patient and Transplantation Characteristics

Characteristic	No. (%)				P[a]
	All Patients Age ≥ 50 Years	Patients Age 50-59 Years	Patients Age 60-69 Years	Patients Age 70-75 Years	
Total patients	271 (100)	115 (42)	129 (48)	27 (10)	
Patient age, years					
Median	61	55	64	72	
Range	50-75	50-59	60-69	70-75	
Male sex	184 (68)[b]	78 (68)	86 (67)	20 (74)	.78
Histology					
Myeloid	100 (37)	39 (34)	50 (39)	11 (41)	.87
Lymphoid	169 (62)	75 (65)	78 (60)	16 (59)	
Biphenotypic	2 (< 1)	1 (< 1)	1 (< 1)	0 (0)	
Diagnosis					
AML	65 (24)[c]	29 (25)	32 (25)	4 (15)	
ALL	9 (3)	5 (4)	4 (3)	0 (0)	
Biphenotypic leukemia	2 (< 1)	1 (< 1)	1 (< 1)	0 (0)	
MDS/MPN	35 (13)	10 (9)	18 (14)	7 (26)	
Aggressive NHL	83 (31)	28 (24)	45 (35)	10 (37)	
Mantle-cell lymphoma	25 (9)	12 (10)	9 (7)	4 (15)	
Indolent NHL or CLL	40 (15)[d]	22 (19)	17 (13)	1 (4)	
HL	7 (3)[e]	4 (3)[e]	3 (2)	0 (0)	
MM	5 (2)	4 (3)	0 (0)	1 (4)	
Time from diagnosis to BMT, years					.04[f]
Median	2.0	2.3	1.5	3.2	
Range	0.2-26.4	0.2-21.2	0.2-23.9	0.4-26.4	
Year of BMT					
2003-2009	122 (45)	63 (55)	51 (40)	8 (30)	.02
2010-2013	149 (55)	52 (45)	78 (60)	19 (70)	
Refined DRI risk group[g]					
Low	44 (16)	25 (22)	15 (12)	4 (15)	.18
Intermediate	183 (68)	76 (66)	88 (68)	19 (70)	
High/very high	44 (16)[h]	14 (12)	26 (20)	4 (15)	
HCT-CI score					
0 (low risk)	67 (25)	35 (30)	27 (21)	5 (19)	.35
1-2 (intermediate risk)	93 (34)	37 (32)	44 (34)	12 (44)	
≥ 3 (high risk)	111 (41)	43 (38)	58 (45)	10 (37)	
Prior autologous BMT	42 (16)	26 (23)	15 (12)	1 (4)	.01
Donor age, years					.01[f]
Median	40	35	40	45	
Range	13-79	13-79	20-73	33-68	
No. of class I and II antigen mismatches[i]					
Median	5				
Range	1-5				
5	143 (53)				
4	73 (27)				
3	40 (15)				
1-2	15 (6)				

Abbreviations: ALL, acute lymphoblastic leukemia or lymphoma; AML, acute myeloid leukemia; BMT, blood or marrow transplantation; CLL, chronic lymphocytic leukemia; DRI, Disease Risk Index; HCT-CI, hematopoietic cell transplantation–specific comorbidity index; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma.

[a]*P* for overall differences between the three age groups.

[b]Percentages are for column-wise comparisons unless otherwise specified.

[c]Excludes biphenotypic leukemia; 30 patients with de novo disease and 35 patients with secondary or therapy-related disease.

[d]Excludes transformed lymphoma; 21 patients with CLL or small lymphocytic lymphoma and 19 patients with other indolent B-cell NHL.

[e]Includes one HL arising from CLL and one lymphocyte-predominant HL.

[f]Kruskal-Wallis test for differences.

[g]Refers to composite of disease risk and stage risk as published.[25]

[h]Thirty-six patients were high risk, and eight patients were very high risk.

[i]Antigen mismatching in any direction; composite of HLA-A, -B, -Cw, -DRB1, and -DQB1.

class II loci, and 89% were DRB1 mismatched. The most common diagnoses were aggressive non-Hodgkin lymphoma (NHL) and acute myeloid leukemia. Most patients (84%) had intermediate-risk or high-/very high–risk disease by refined DRI grouping. All patients with lymphoma had factors that were thought to make cure with autologous BMT unlikely. Of 27 patients with de novo diffuse large B-cell lymphoma, nine (33%) received prior autologous BMT; in most others, allogeneic BMT was prioritized because of short initial

Table 2. Outcome Probabilities After Nonmyeloablative HLA-Haploidentical BMT With High-Dose Post-Transplantation Cyclophosphamide in Patients Age 50 to 75 Years

Outcome	Probability (%; 95% CI)				P*
	All Patients Age ≥ 50 Years (N = 271)	Patients Age 50 to 59 Years (n = 115)	Patients Age 60 to 69 Years (n = 129)	Patients Age 70 to 75 Years (n = 27)	
CuI of count recovery					
Neutrophils, 500/μL					.40
Day 30	90 (86 to 93)	90 (85 to 96)	88 (83 to 94)	93 (81 to 100)	
Platelets, 20,000/μL					.62
Day 60	85 (81 to 90)	86 (80 to 93)	84 (77 to 90)	89 (76 to 100)	
CuI of acute GVHD					
Grade 2-4					.009
Day 180	33 (27 to 39)	24 (16 to 31)	37 (29 to 46)	52 (32 to 71)	
Grade 3-4					.53
Day 180	3 (1 to 5)	4 (0 to 7)	3 (0 to 6)	0 (0 to 0)	
CuI of chronic GVHD					.45
1 year	10 (6 to 13)	8 (3 to 13)	11 (6 to 17)	12 (0 to 25)	
CuI of NRM					.20
Day 100	6 (3 to 9)	4 (1 to 8)	8 (3 to 12)	7 (0 to 17)	
Day 180	8 (5 to 12)	8 (3 to 13)	9 (4 to 14)	7 (0 to 17)	
1 year	12 (8 to 16)	10 (4 to 15)	14 (8 to 20)	11 (0 to 23)	
CuI of relapse					.80
1 year	37 (31 to 43)	39 (30 to 48)	37 (29 to 45)	33 (15 to 52)	
3 years	46 (40 to 52)	48 (38 to 57)	46 (37 to 55)	41 (19 to 64)	
PFS					.65
1 year	51 (45 to 57)	51 (43 to 61)	50 (42 to 59)	56 (40 to 78)	
3 years	37 (31 to 43)	39 (31 to 49)	35 (27 to 45)	33 (17 to 63)	
DFS					.63
1 year	50 (45 to 57)	51 (43 to 61)	49 (41 to 58)	52 (36 to 75)	
3 years	36 (31 to 43)	39 (31 to 49)	34 (26 to 44)	34 (18 to 64)	
OS					.66
1 year	65 (60 to 71)	64 (56 to 74)	66 (58 to 74)	67 (51 to 87)	
3 years	46 (40 to 53)	48 (39 to 59)	45 (36 to 55)	44 (28 to 70)	

Abbreviations: BMT, blood or marrow transplantation; CuI, cumulative incidence; DFS, disease-free survival; GVHD, graft-versus-host disease; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival.
*P for overall differences between the three age groups based on stratified log-rank or Gray's k-sample tests, with stratification by BMT year (2003 to 2009 *v* later).

remission or chemotherapy refractoriness. Of seven Hodgkin lymphomas, four had treatment failure with autologous BMT, one was chemotherapy refractory, one was lymphocyte predominant, and one arose in the setting of chronic lymphocytic leukemia.

When grouped by decade, the three patient age groups had similar histology (percent myeloid *v* lymphoid) and HCT-CI risk categories. Older donor age was statistically significantly associated with older patient age (Table 1). All but one of the transplantations in patients age ≥ 70 occurred after 2007.

Overall and age-specific outcomes are listed in Table 2, and disease-specific outcomes are listed in Table 3. The median follow-up time was 4.0 years (range, 0.02 to 10.2 years) overall by the reverse Kaplan-Meier method and 3.2 years (range, 0.4 to 10.2 years) among survivors. There was a 90% probability of neutrophil recovery by day 30 (median, 17 days) and an 85% probability of platelet recovery ≥ 20,000/μL by day 60 (median, 25 days). Primary or secondary graft failure occurred in 16 (6.0%) of 266 evaluable patients (95% CI, 3.5% to 9.6%), each having autologous neutrophil recovery. The estimated day 180 CuIs of grade 2 to 4 and grade 3 to 4 acute GVHD were 33% and 3%, respectively (Fig 1A). The estimated 1-year CuI of any chronic GVHD was 10% (Fig 1B). Among all patients age ≥ 50 years, the estimated CuI of NRM was 8% at day 180 and 12% at 1 year (Fig 1C). The 1-year PFS and OS probabilities were 51% and 65%, respectively, with 3-year probabilities of 37% and 46%, respectively (Fig 1D).

Count Recovery and GVHD

Neutrophil and platelet recovery times were similar among the age groups (Table 2). On univariable analysis, older patient age was statistically significantly associated with a higher incidence of grade 2 to 4 acute GVHD (Table 2, Fig 2A). When stratified by donor age (≥ *v* < 40 years) and BMT year, the subdistribution hazard ratio (SDHR) for grade 2 to 4 acute GVHD was statistically significantly higher in patients age ≥ 60 years (SDHR, 1.67; 95% CI, 1.05 to 2.65; $P = .03$) compared with patients age 50 to 59 years. Stratification by donor age ≥ 50 versus < 50 years yielded similar results, as did treating donor age as a continuous covariate (data not shown). No statistically significant association was detected between older patient age (relative to ages 50 to 59 years) and grade 3 or 4 acute or chronic GVHD (Table 2, Fig 2B).

Nonrelapse Morbidity and NRM

The estimated CuIs of NRM for patients in their 50s, 60s, and 70s were 8%, 9%, and 7%, respectively, at day 180, with 1-year NRM estimates of 9%, 14%, and 11%, respectively (Table 2, Fig 2C; $P = .20$).

Table 3. Disease-Specific Outcomes of Nonmyeloablative HLA-Haploidentical BMT With High-Dose Post-Transplantation Cyclophosphamide in Patients Age 50 to 75 Years

Disease and Age Group	No. of Patients	Median Months to Relapse (range)*	Probability (%; 95% CI)							
			Relapse		PFS		DFS		OS	
			1 Year	3 Years	1 Year	3 Years	1 Year	3 Years	1 Year	3 Years
AML										
≥ 50 years	65	6.0 (1.0-45.5)	42 (29 to 54)	52 (39 to 65)	52 (41 to 66)	40 (29 to 54)	52 (41 to 66)	40 (29 to 54)	64 (53 to 77)	49 (37 to 64)
≥ 60 years	36	—	47 (31 to 64)	60 (43 to 77)	47 (33 to 67)	31 (19 to 52)	47 (33 to 67)	31 (19 to 52)	66 (52 to 84)	38 (24 to 60)
NHL										
≥ 50 years	148†	4.7 (0.8-94.0)	32 (24 to 39)	39 (31 to 48)	52 (45 to 61)	38 (31 to 48)	51 (44 to 60)	38 (31 to 47)	65 (58 to 73)	47 (39 to 56)
≥ 60 years	86	—	27 (17 to 36)	34 (24 to 44)	53 (44 to 65)	39 (30 to 52)	52 (43 to 64)	38 (29 to 51)	66 (57 to 77)	49 (39 to 62)
Aggressive NHL										
≥ 50 years	83	4.2 (0.8-94.0)	34 (23 to 44)	40 (29 to 52)	54 (44 to 66)	39 (30 to 52)	55 (46 to 67)	39 (30 to 52)	69 (59 to 79)	47 (37 to 60)
≥ 60 years	55	—	27 (15 to 39)	36 (22 to 50)	56 (45 to 71)	38 (27 to 55)	56 (45 to 71)	38 (27 to 55)	69 (58 to 82)	51 (38 to 66)
Indolent NHL or MCL										
≥ 50 years	65‡	5.5 (0.8-25.7)	29 (18 to 40)	38 (26 to 50)	49 (38 to 63)	37 (27 to 51)	46 (35 to 60)	36 (26 to 50)	60 (49 to 73)	46 (35 to 60)
≥ 60 years	31	—	26 (10 to 42)	30 (13 to 46)	48 (34 to 70)	41 (27 to 63)	45 (31 to 67)	38 (24 to 60)	61 (46 to 81)	47 (32 to 69)

Abbreviations: AML, acute myeloid leukemia; BMT, blood or marrow transplantation; DFS, disease-free survival; MCL, mantle-cell lymphoma; NHL, non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival.
*Months from BMT to relapse/progression or unplanned treatment of disease persistence in patients with such events.
†Including chronic lymphocytic leukemia/small lymphocytic lymphoma.
‡Excluding transformation; 19 patients with indolent B-cell NHL excluding small lymphocytic lymphoma, 21 patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, and 25 patients with MCL.

Given the limited number of patients age ≥ 70 years, outcomes in patients age 60 to 75 years (n = 156) were also evaluated. In patients age ≥ 60 years, the estimated CuI of NRM was 9% (95% CI, 4% to 13%) at day 180 and 13% (95% CI, 8% to 19%) at 1 year ($P = .08$ *v* ages 50 to 59 years). On univariable analysis (Table 4), patients age ≥ 60 years were at higher risk of NRM. However, statistically significant differences were not detected (for age ≥ 60 years relative to age 50 to 59 years: SDHR, 1.71; 95% CI, 0.94 to 3.10; $P = .08$). Univariable analyses of NRM with age as a continuous variable were similar (for every 10-year age increase, SDHR, 1.44; 95% CI, 0.93 to 2.22; $P = .10$).

In this population, higher HCT-CI risk categories were not statistically significantly associated with greater NRM by predefined risk categories (low, intermediate, or high risk; Table 4), although there was a statistically significant effect with HCT-CI score treated as a continuous variable (data not shown). The effect seemed predominantly confined to HCT-CI scores of ≥ 5 relative to lower scores.

Hospitalization data up through day 60 and post-transplantation ECOG PS are shown for descriptive purposes in Appendix Table A1 (online only). The oldest patients were significantly more likely to be electively hospitalized for BMT. In patients not electively hospitalized, the median time to first hospitalization was 9 days, with an associated 3-day median length of stay. Nineteen (7%) of 271 patients were mechanically intubated in the first 60 days after BMT, with no statistically significant difference among patients who received transplantation in their 50s, 60s, and 70s. At approximately 6 months and approximately 1 year after transplantation, the majority of relapse-free patients had an ECOG PS ≤ 1. The PS distribution (≤ 1, 2, or ≥ 3) at these time points was comparable between the age groups.

Relapse, PFS, and OS

Disease-specific outcomes for the largest groups are listed in Table 3. In patients with acute myeloid leukemia age ≥ 50 years (n = 65), the 3-year probabilities of relapse, PFS, and OS were 52%, 40%, and 49%, respectively (Fig 1E). In patients with NHL age ≥ 50 years (n = 148), including patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, the 3-year probabilities of relapse, PFS, and OS were 39%, 38%, and 47%, respectively (Fig 1F). In patients with aggressive B- or T- cell NHL (n = 83), the 3-year estimates of relapse, PFS, and OS were 40%, 39%, and 47%, respectively.

For the group overall, the estimated 3-year CuIs of relapse for patients in their 50s, 60s, and 70s were 48%, 46%, and 41%, respectively (Table 2, Fig 2D; $P = .80$). On univariable analysis (Table 4), there was no statistically significant association between older patient age and relapse risk in this study cohort.

The 3-year PFS probabilities for patients in their 50s, 60s, and 70s were 38%, 35%, and 33%, respectively (Table 2, Fig 2E; $P = .65$), with 3-year OS probabilities of 48%, 45%, and 44%, respectively (Fig 2F; $P = .66$). Similar to patients age 50 to 59 years, patients aged ≥ 60 years had 1- and 3-year PFS probabilities of 51% (95% CI, 43% to 59%) and 35% (95% CI, 28% to 44%; $P = .41$), respectively, with OS probabilities of 66% (95% CI, 59% to 74%) and 44% (95% CI, 36% to 54%; $P = .36$), respectively. In univariable analyses of PFS and OS (Table 4), no statistically significant association was seen with older patient age treated as either a categorical variable (relative to age 50 to 59 years) or continuous variable.

The DRI was developed to provide a robust tool to improve interpretation of clinical data involving a variety of allogeneic BMT patients and has successfully risk stratified heterogeneous adult patient cohorts across diseases and disease status.[25] In low-, intermediate-, and high-/very high–risk disease groups based on the refined DRI,[25] the 3-year PFS probabilities were 62% (95% CI, 49% to 79%), 36% (95% CI, 29% to 44%), and 15% (95% CI, 7% to 32%; $P < .001$), and the 3-year OS probabilities were 68% (95% CI, 55% to 84%), 44% (95% CI, 37% to 53%), and 31% (95% CI, 20% to 49%; $P < .001$), respectively. After adjustment for refined DRI group (Table 4), there remained no statistically significant association between older patient age and PFS, OS, or relapse.

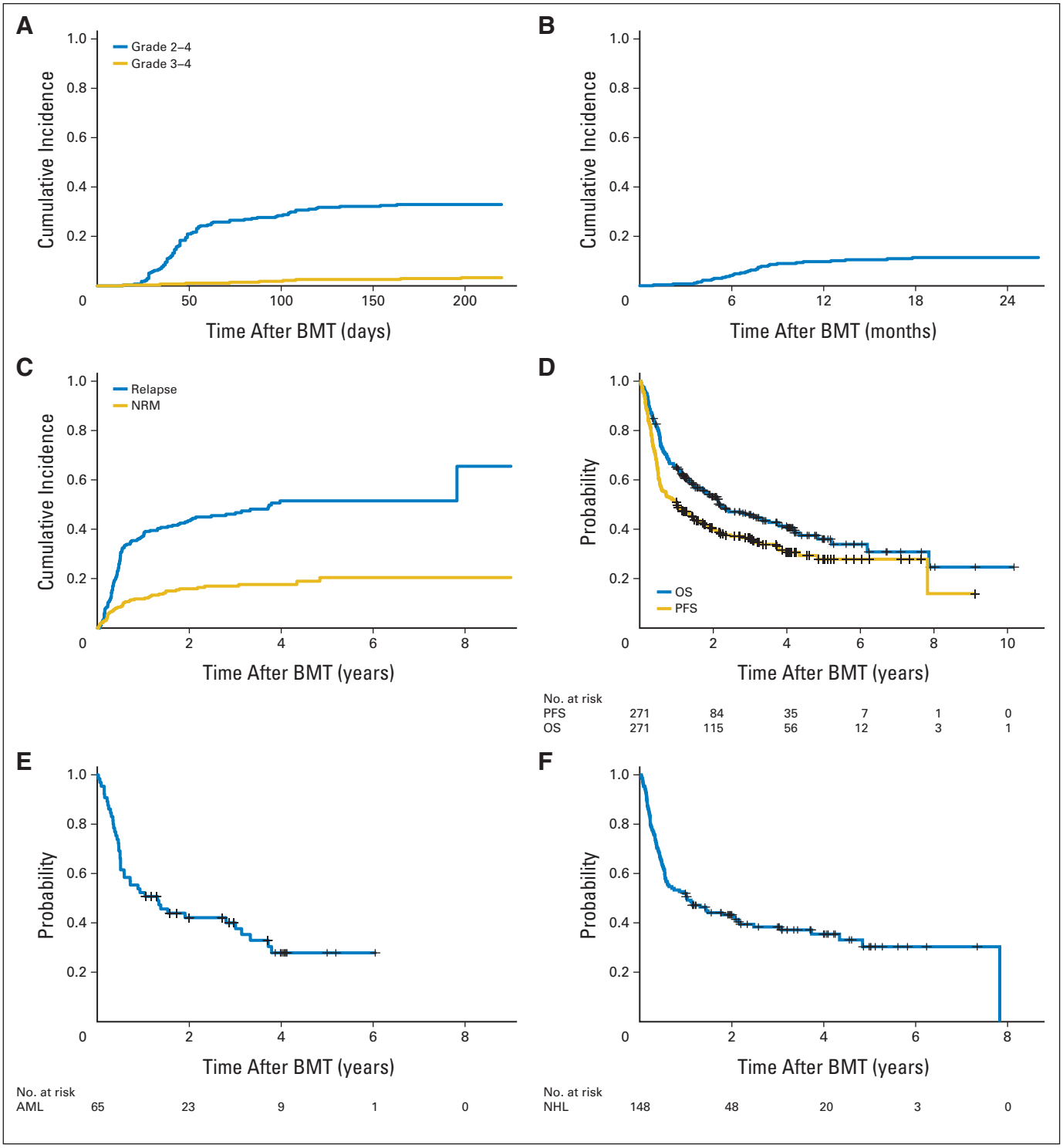

Fig 1. Outcomes of nonmyeloablative haploidentical blood or marrow transplantation (BMT) with high-dose post-transplantation cyclophosphamide in patients age 50 to 75 years. Cumulative incidences of (A) acute graft-versus-host disease (GVHD), (B) any chronic GVHD, and (C) nonrelapse mortality (NRM) and relapse estimated by competing-risk analyses. (D) Progression-free survival (PFS) and overall survival (OS). (E) PFS in acute myeloid leukemia (AML; n = 65). (F) PFS in non-Hodgkin lymphoma (NHL; n = 148) including chronic lymphocytic leukemia/small lymphocytic lymphoma. Point estimates are listed in Tables 2 and 3.

DISCUSSION

With the increasing life expectancy of the general population, the burden of hematologic cancers is expected to rise substantially, particularly among older adults.[20] By reducing regimen-related toxicity,[33] the use of NMA or RIC conditioning broadens the applicability of allogeneic BMT, including to those ineligible for myeloablative conditioning as a result of age, comorbidities, or extent of prior therapy. However, NMA allogeneic BMT has been underused in elderly patients,[34] in part because of toxicity concerns. The reduced likelihood of having a

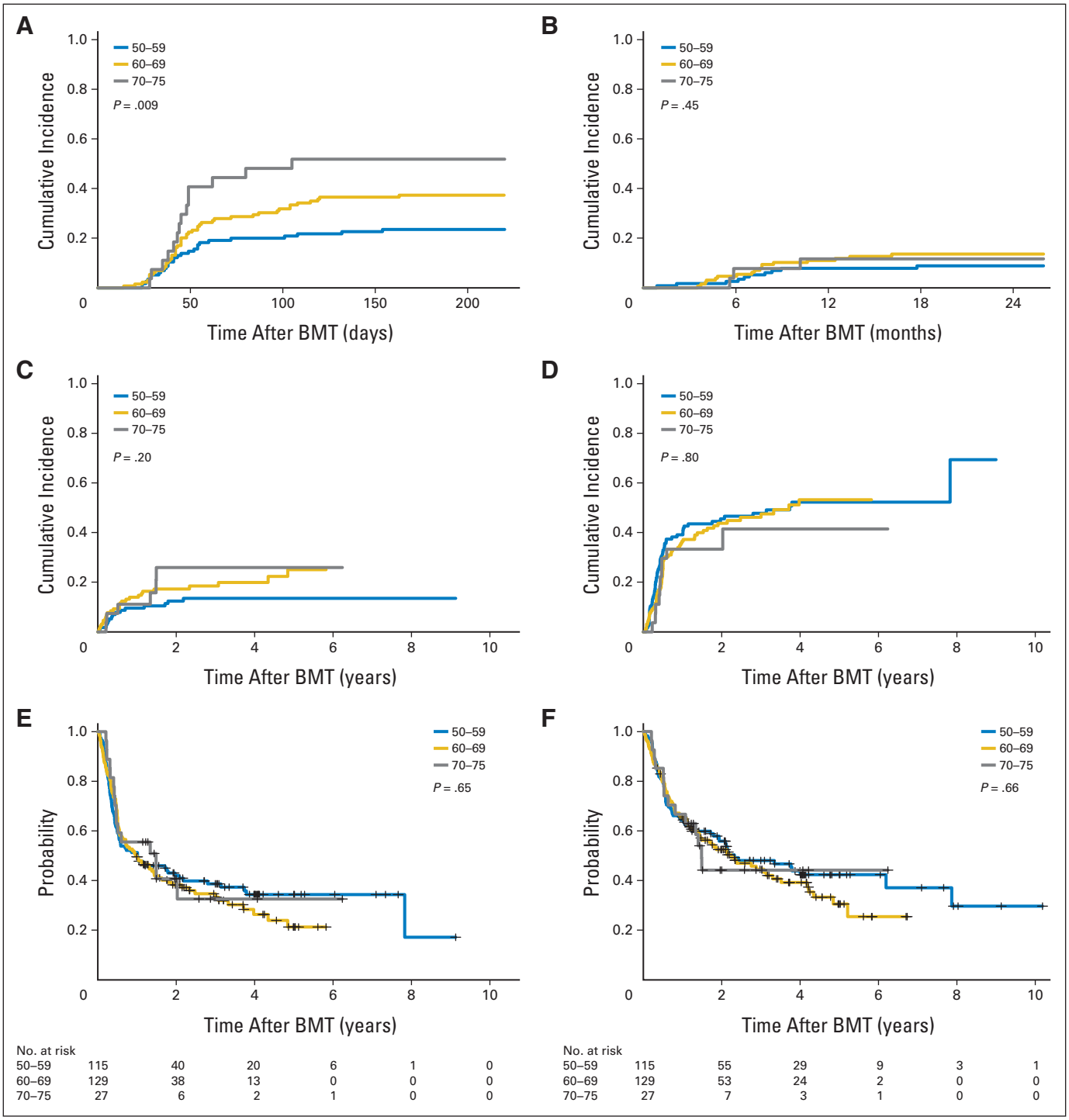

Fig 2. Age-specific outcomes of nonmyeloablative HLA-haploidentical blood or marrow transplantation (BMT) with high-dose post-transplantation cyclophosphamide, with patient age grouped by decade. Cumulative incidences of (A) acute grade 2 to 4 graft-versus-host disease (GVHD), (B) any chronic GVHD, (C) nonrelapse mortality, and (D) relapse estimated by competing-risk analyses. (E) Progression-free survival. (F) Overall survival. Point estimates are listed in Table 2.

suitable HLA-matched sibling donor also likely contributes to the underutilization of allogeneic BMT in older patients.

Notably, this study suggests that advanced age is not associated with prohibitive toxicities in older adults undergoing NMA haplo-BMT with PTCy. In fact, there was no apparent decrement in PFS or OS in patients age ≥ 60 years, and even patients age 70 to 75 years, when compared with patients in their 50s. Unquestionably, the older patients were a selected group in that they needed to be otherwise fit for BMT, and it is likely that fewer older patients receive transplants because of comorbidities. However, in older patients who actually underwent BMT, hematopoietic recovery was brisk, with an estimated 90% of all patients age ≥ 50 years achieving neutrophil recovery by

Table 4. Regression Models of Outcomes After Nonmyeloablative HLA-Haploidentical BMT in Patients Age 50 to 75 Years

	NRM		Relapse		PFS		OS	
Variable	SDHR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Univariable analyses*								
Older patient age (per 10 years of age)†	1.44 (0.93 to 2.22)	.10	0.99 (0.75 to 1.30)	.94	1.13 (0.89 to 1.42)	.31	1.20 (0.93 to 1.54)	.16
Patient age, years								
50-59	Ref		Ref		Ref		Ref	
60-69	1.67 (0.90 to 3.10)	.11	0.96 (0.67 to 1.39)	.83	1.16 (0.84 to 1.59)	.36	1.17 (0.83 to 1.64)	.37
70-75	1.94 (0.77 to 4.85)	.16	0.78 (0.39 to 1.55)	.48	1.04 (0.60 to 1.80)	.90	1.14 (0.64 to 2.06)	.66
Patient age, years								
50-59	Ref		Ref		Ref		Ref	
≥ 60	1.71 (0.94 to 3.10)	.08	0.93 (0.65 to 1.33)	.70	1.14 (0.84 to 1.55)	.41	1.17 (0.84 to 1.62)	.36
Refined DRI risk group								
Low	Ref		Ref		Ref		Ref	
Intermediate	1.30 (0.59 to 2.85)	.51	2.53 (1.31 to 4.89)	.006	2.44 (1.47 to 4.07)	< .001	2.29 (1.33 to 3.95)	.003
High/very high	0.70 (0.23 to 2.15)	.54	5.09 (2.54 to 10.21)	< .001	3.71 (2.09 to 6.58)	< .001	3.22 (1.74 to 5.96)	< .001
HCT-CI score								
0 (low risk)	Ref						Ref	
1-2 (intermediate risk)	1.19 (0.52 to 2.71)	.68					1.04 (0.68 to 1.60)	.84
≥ 3 (high risk)	1.77 (0.83 to 3.75)	.14					1.20 (0.80 to 1.80)	.38
Older donor age (per 10 years of age)†	1.08 (0.91 to 1.29)	.38	1.00 (0.88 to 1.14)	.97	1.05 (0.94 to 1.16)	.40	1.05 (0.93 to 1.17)	.44
DRI-adjusted models*‡								
Patient age, years								
50-59			Ref		Ref		Ref	
≥ 60			0.81 (0.57 to 1.17)	.26	1.00 (0.73 to 1.36)	.98	1.02 (0.73 to 1.43)	.89
Refined DRI risk group								
Low			Ref		Ref		Ref	
Intermediate			2.59 (1.34 to 5.02)	.005	2.45 (1.46 to 4.08)	< .001	2.28 (1.32 to 3.95)	.003
High/very high			5.36 (2.63 to 10.89)	< .001	3.71 (2.07 to 6.64)	< .001	3.19 (1.71 to 5.97)	< .001

Abbreviations: BMT, blood or marrow transplantation; DRI, Disease Risk Index; HCT-CI, hematopoietic cell transplantation–specific comorbidity index; HR, hazard ratio; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival; Ref, reference; SDHR, subdistribution hazard ratio.
*Stratified by BMT year (2003 to 2009 *v* later).
†Continuous variable.
‡Models with age as a continuous rather than categorical variable were similar.

day 30 (Table 2). The estimated 6-month CuI of NRM was 7% (95% CI, 0% to 17%) in patients age 70 to 75 years and 8% (95% CI, 3% to 13%) in patients age 50 to 59 years. Time-to-event curves for relapse, PFS, and OS were likewise superimposable (Fig 2). Older donor age may contribute to the higher incidence of grade 2 to 4 acute GVHD observed with increasing patient age.[35] However, the probabilities of severe acute GVHD and any chronic GVHD were low, regardless of age group. In this cohort, relapse rather than toxicity was the leading cause of treatment failure. Rather than older age, disease type and pretransplantation disease status, as determined by the DRI,[25] were key determinants of overall outcome in this study.

The study has a number of limitations, including those inherent to a retrospective single-institution analysis. Selection bias may have influenced inferences from the data. Transplantations in older patients occurred more recently, and regression models, although stratified by BMT year, may not have accounted for some time-related factors. Sample size limitations, particularly for the oldest age group, may mask smaller differences in outcomes, especially for toxicities with relatively low incidences such as NRM. In addition, more comprehensive metrics of transplantation-related toxicity would be helpful, including geriatric assessment measures of functionality, cognition, and quality of life that are best studied prospectively.[36,37] Nevertheless, we find these outcomes in older adults quite encouraging.

NMA haplo-BMT with PTCy seems to produce results in older patients that compare favorably with those reported with NMA or RIC HLA-matched BMT.[33,38-41] For example, in a large Center for International Blood and Marrow Transplant Research analysis of RIC or NMA BMT (> 90% HLA matched), patients age ≥ 40 years had a 33% to 36% probability of acute GVHD, and patients age ≥ 65 years had an estimated 1-year NRM of 30% to 35%.[38] In another study of NMA BMT, also more than 90% HLA matched, patients age ≥ 60 years had an estimated 1-year NRM of 20%, with no apparent relationship between age group and either NRM or survival.[40]

This study suggests that, at least with PTCy-based platforms, NMA haplo-BMT should be considered for older adults who lack HLA-matched donors but who otherwise meet eligibility criteria for BMT. Our institution no longer has an upper age limit for NMA haplo-BMT with PTCy. Strategies to treat and reduce disease relapse are intensively being studied. We found that haploidentical donor lymphocyte infusions have similar effectiveness and toxicity profiles to HLA-matched donor lymphocyte infusions.[42] The favorable toxicity profile of the PTCy platform can also facilitate novel post-transplantation approaches for relapse reduction.[43]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Outcomes of Nonmyeloablative HLA-Haploidentical Blood or Marrow Transplantation With High-Dose Post-Transplantation Cyclophosphamide in Older Adults

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

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Patents, Royalties, Other Intellectual Property: Infusion of Transiently Engrafting, Selected Populations of Allogeneic Lymphocytes to Treat Cancer Inventors: Ephraim J. Fuchs, Lode Swinnen, Heather J. Symons C12021. Licensed to Immunova. (Inst)

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Appendix

Table A1. Descriptive Outcomes of Nonmyeloablative HLA-Haploidentical BMT in Relation to Patient Age

Outcome	All Patients Age 50-75 Years	Patients Age 50-59 Years	Patients Age 60-69 Years	Patients Age 70-75 Years
Total patients, No.	271	115	129	27
Electively hospitalized for BMT, No. (%)	8 (3)	0 (< 1)	4 (3)	4 (15)*
Not electively hospitalized, No. (%)	263	115	125	23
Hospital days until day 60				
0	105 (40)	52 (45)	45 (36)	8 (35)
1-7	95 (35)	41 (36)	46 (37)	8 (35)
> 7	63 (24)	22 (19)	34 (27)	7 (30)
Median stay, days	6	5	7	7
Range, days	1-57	1-51	1-57	2-51
Days of intubation until day 60, No. (%)				
0	252 (93)	110 (96)	118 (91)	24 (89)†
≥ 1	19 (7)	5 (4)	11 (9)	3 (11)
Status at day 180 ± 1 month, No. (%)				
Relapse free	188	78	92	18
PS 0 or 1	137 (73)	56 (72)	67 (73)	14 (78)
PS 2	17 (9)	7 (9)	9 (10)	1 (6)
PS 3 or 4	7 (4)	3 (4)	3 (3)	1 (6)
PS not evaluable	5 (3)	3 (4)‡	2 (2)‡	0 (0)
NRM	22 (12)	9 (12)	11 (12)	2 (11)
Relapse or relapse death	83	37	37	9
Status at day 365 ± 2 months, No. (%)				
Relapse free	166	68	80	18
PS 0 or 1	112 (67)	51 (75)	48 (60)	13 (72)
PS 2	12 (7)	4 (6)	7 (9)	1 (6)
PS 3 or 4	5 (3)	1 (1)	4 (5)	0 (0)
PS not evaluable	6 (4)	1 (1)§	4 (5)‡	1 (6)§
NRM	31 (19)	11 (16)	17 (21)	3 (17)
Relapse or relapse death	105	47	49	9

Abbreviations: BMT, blood or marrow transplantation; NRM, nonrelapse mortality; PS, Eastern Cooperative Oncology Group performance status.
*$P < .001$ for comparison between age groups.
†$P = .32$ for comparison between age groups.
‡Not evaluable within the designated window.
§PS < 3.