Biol Blood Marrow Transplant 25 (2019) 86–93

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

The Impact of Advanced Patient Age on Mortality after Allogeneic Hematopoietic Cell Transplantation for Non-Hodgkin Lymphoma: A Retrospective Study by the European Society for Blood and Marrow Transplantation Lymphoma Working Party

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Article history:
Received 4 March 2018
Accepted 24 August 2018

Key Words:
Allogeneic hematopoietic cell transplantation
Non-Hodgkin lymphoma
Age

A B S T R A C T

More than 60% of patients with non-Hodgkin lymphoma (NHL) are age >60 years at presentation. The purpose of this study was to compare the potential risks and benefits of allogeneic hematopoietic cell transplantation (alloHCT) in elderly patients with NHL with younger patients in a large sample, also taking into account comorbidity information. All patients age ≥18 years who had undergone alloHCT from a matched sibling or unrelated donor for NHL between 2003 and 2013 and were registered with the European Society for Blood and Marrow Transplantation were eligible for the study. The primary study endpoint was 1-year nonrelapse mortality (NRM). A total of 3919 patients were eligible and were categorized by age: young (Y), 18 to 50 y (n = 1772); middle age (MA), 51 to 65 y (n = 1967); or old (O), 66 to 77 y (n = 180). Follicular lymphoma was present in 37% of the patients; diffuse large B cell lymphoma, in 30%; mantle cell lymphoma, in 21%, and peripheral T cell lymphoma, in 11%. At the time of alloHCT, 85% of the patients were chemosensitive and 15% were chemorefractory. With a median follow-up of 4.5 years in survivors, NRM at 1 year was 13% for the Y group. 20% for the MA group, and 33% for the O group (P <.001), whereas relapse incidence and overall survival (OS) at 3 years in the 3 groups were 30%, 31%, and 28% (P = .355) and 60%, 54%, and 38% (P <.001), respectively. Multivariable adjustment for confounders, including sex, NHL subset, time from diagnosis, chemosensitivity, donor, and conditioning, confirmed older age as a significant predictor for NRM and OS, but not for relapse risk. Although comorbidity was a significant predictor of NRM in a subset analysis restricted to the 979 patients with comorbidity information available, age retained its significant impact on NRM. In conclusion, our data show that alloHCT in patients age >65 y provides similar NHL control as seen in younger patients but is associated with a higher NRM that is not fully explained by comorbidity. Thus, although alloHCT is feasible and effective in very old patients, the increased NRM risk must be taken into account when assessing the indication for alloHCT for NHL in this age group.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a disease of the elderly. Except for Burkitt lymphoma, the age peak for NHL, including the most common subsets diffuse large B cell lymphoma

Financial disclosure: See Acknowledgments on page 92.

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https://doi.org/10.1016/j.bbmt.2018.08.025
1083-8791/

(DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and peripheral T cell lymphoma (PTCL), is after 65 years (http: //seer.cancer.gov/registries/terms.html) [1]. Although standard first-line and salvage strategies, including chemotherapy, chemoimmunotherapy, targeted therapy, and autologous hematopoietic cell transplantation (HCT), may result in sustained disease control or even cure in many patients, a variable proportion of patients with NHL will fail these treatments and thus need more effective therapy.

Allogeneic HCT (alloHCT) has been proven to be effective in relapsed and refractory (R/R) NHL and is considered a standard option in distinct indications of advanced DLBCL, FL, MCL, and PTCL [2-13]. With the advent of reduced-intensity conditioning (RIC) strategies and other improvements in transplantation technology, alloHCT is being increasingly considered in elderly patients with R/R NHL. In the European Society for Blood and Marrow Transplantation (EBMT) registry, the proportion of patients age 51 to 70 years undergoing alloHCT for NHL has increased from 8% in 1991-1995 to 23% in 1996-2000, 38% in 2001-2005, 52% in 2006-2010 .and 58% in 2011-2015 (EBMT, data on file). Similar observations have been reported by the Center for International Blood and Marrow Transplant Research (CIBMTR) [14]. However, the available evidence on safety and efficacy of alloHCT in NHL is largely restricted to patients age <60 and those without comorbidities. Data on the outcomes of alloHCT in elderly patients with NHL are sparse [15]. The purpose of this study was to compare the potential risks and benefits of alloHCT for NHL between elderly patients and younger patients in a large sample, also taking into account comorbidity information.

PATIENTS AND METHODS

Data Source

The EBMT is a voluntary organization comprising more than 600 transplantation centers located mainly in Europe. Accreditation as a member center requires submission of minimal essential data (MED-A form) from all consecutive patients, including diagnosis of underlying disease and type of transplantation, to a central registry. Informed consent for transplantation and data collection was obtained locally according to regulations applicable at the time of transplantation. Since January 1, 2003, all transplantation centers have been required to obtain written informed consent before data registration with the EBMT, in accordance with the Declaration of Helsinki of 1975.

Study Design

In this retrospective EBMT registry-based analysis, all patients age ≥18 years who had undergone alloHCT from a matched sibling or unrelated donor for FL, DLBCL, MCL, or PTCL between 2003 and 2013 and were registered with the EBMT were eligible. Patients allografted with a cord blood or haploidentical transplant were excluded. All patient-, disease-, and transplantation-related data used in this study were collected from EBMT MED-A standard forms. Because comorbidity information was not a compulsory item on the MED-A versions used during the study period, it was available for only a subset of the entire patient sample. Therefore, the study was split into an analysis of the entire sample and a second analysis of the subset with comorbidity information available ,including this variable as covariate in multivariable risk factor assessments.

Statistical Analysis

The primary study outcome was 1-year nonrelapse mortality (NRM), defined as the time from alloHCT to death in the absence of previous relapse or progression. Secondary outcomes were progression-free survival (PFS), defined as the time from alloHCT to disease relapse or progression or death from any cause, whatever occurs first; overall survival (OS), defined as the time from alloHCT to death from any cause; relapse incidence (RI), defined as time from alloHCT to relapse or progression (taking into account NRM as a competing risk); and incidences of acute and chronic graft-versus-host disease (GVHD).

Survival curves for OS and PFS were estimated by the Kaplan-Meier method and compared between groups using the log-rank test. To account for the competing-risk structure of the event, cumulative incidence curves were estimated for engraftment, NRM, RI, and acute and chronic GVHD (with PFS as a competing event for both acute and chronic GVHD) and compared between groups using Gray's test. Multivariate assessment of prognostic factors associated with OS and PFS using Cox regression models was performed. The effects of age categories on survival endpoints after multivariate adjustment for confounders, as represented by available MED-A baseline information (i.e., underlying diagnosis, chemosensitivity at alloHCT, donor-recipient sex match, donor type, time from diagnosis to alloHCT, conditioning intensity [RIC/myeloablative conditioning [MAC], total body irradiation [TBI] in the conditioning regimen, graft source [bone marrow versus peripheral blood (PB)], comorbidities [yes/no], and T cell depletion [TCD]), were performed using Cox regression models. In addition, an inverse probability weighting (IPW) method was used to calculate an adjusted hazard ratio for each age category and its effect on OS and to estimate adjusted survival curves. Variables used to calculate the weighting were the same as used in the Cox models. Multivariate assessment of prognostic factors associated with NRM and RI was performed using cause-specific Cox models. Calculations were done using R version 3.1 with the R packages coin version 1.0.19, rms version 3.3-0, cmprsk version 2.2-2, and kmi version 0.3-4 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were 2-sided, with a P value <.05 considered to indicate a statistically significant result.

RESULTS

Patients

A total of 3919 patients were identified in the EBMT registry who met our inclusion criteria for this study, including 1772 patients in the young (Y) group (18 to 50 years), 1967 patients in the middle aged (MA) group (51 to 65 years), and 180 patients in the old (O) group (66 to 77 years). The disease distribution included 37% (n = 1461) with FL, 30% (n = 1192) with DLBCL, 21% (n = 823) with MCL, and 11% (n = 443) with PTCL. Approximately 85% (n = 3342) were chemosensitive and 15% (n = 577) were chemorefractory at the time of alloHCT. Age categories were comparable for sex, disease status at transplantation, and performance status; however, compared with Y patients, MA patients had a significant overrepresentation of MCL, unrelated donors, and RIC. These overrepresentations were even more pronounced in O patients. Patient characteristics are summarized by age category in Table 1.

Engraftment and GVHD by Age Category

The cumulative incidence of engraftment at day 100 was 97% (96% to 98%) for Y patients, 97% (96% to 97%) for MA patients, and 92% (86% to 95%) for O patients (P = .024). The cumulative incidence of acute GVHD grade II-IV at day 100 was 27% (25% to 30%) for Y patients, 29% (27% to 31%) for MA patients, and 24% (18% to 31%) for O patients (P = .475). The cumulative incidence of chronic GVHD at 3 years was 49% (46% to 52%) for Y patients, 49% (46% to 52%) for MA patients, and 49% (38% to 56%) for O patients (P = .981).

Survival by Age Category

With a median follow-up for survivors of 4.5 years (IQR, 2 to 7.5 years), NRM for Y, MA and O patients was 13% (12% to 15%) in the Y group, 20% (18% to 22%) in the MA group, and 33% (26% to 41%) in the O group at 1 year post-transplantation, and 18% (16% to 20%), 26% (24% to 29%), 44% (35% to 52%), respectively, at 3 years post-transplantation (P < .001). In contrast, there was no significant difference in relapse risk across the age categories, with a 1-year RI of 24% (22% to 26%) for the Y group, 23% (21% to 25%) for the MA group, and 18% (12% to 24%) for the O group and 3-year RIs of 30% (28% to 33%), 31% (29% to 33%), and 28% (20% to 36%), respectively (P = .355). This translated into a 3-year PFS of 51% (49% to 54%) for the Y group, 42% (40% to 45%) for the MA group, and 29% (21% to 38%) for the O group (P < .01), and respective unadjusted 3-year OS of 60% (58% to 63%), 54% (52% to 56%), and 38% (31% to 47%) (P < .001) (Figure 1). Multivariable adjustment for confounders, including underlying diagnosis, chemosensitivity at alloHCT, donor-recipient sex match, donor type, time from diagnosis to

Table 1
Patient Characteristics by Age Category

Characteristic	Entire cohort (N = 3919)	Y Group (18-50 yr) (N = 1772)	MA Group (51-65 yr) (N = 1967)	O Group (>65 yr) (N = 180)	*P* Value
Age at alloHCT, yr, median (IQR)	51 (43-58)	42 (37-47)	57 (53-60)	67 (66-68)	—
Male sex, n (%)	2535 (65)	1134 (64)	1285 (65)	116 (64)	.69
Diagnosis, n (%)					**<.0001**
DLBCL	1192 (30)	631 (36)	511 (26)	50 (28)	
FL	1461 (37)	684 (39)	730 (37)	47 (26)	
MCL	823 (21)	200 (11)	553 (28)	70 (39)	
PTCL	443 (11)	257 (15)	173 (9)	13 (7)	
Time from diagnosis to alloHCT, mo, median (IQR)	31 (15-59)	25 (13-49)	36 (18-65)	37 (20-68)	**<.0001**
Previous autologous HCT, n (%)	2535 (65)	748 (42)	964 (49)	97 (54)	**<.0001**
Disease status at alloHCT, n (%)					.079
Chemosensitive	3342 (85)	1487 (84)	1702 (87)	153 (85)	
Chemorefractory	577 (15)	285 (16)	265 (13)	27 (15)	
Karnofsky Performance Score, n (%)					.19
Good (≥80)	3352 (85)	1497 (84)	1695 (86)	160 (89)	
Poor (<80)	237 (6)	115 (6)	110 (6)	12 (7)	
Unknown	330 (8)	160 (9)	162 (8)	8 (4)	
Donor, n (%)					**<.0001**
Identical sibling	2468 (63)	1190 (67)	1212 (62)	66 (37)	
Unrelated	1451 (37)	582 (33)	755 (38)	114 (63)	
Graft source, n (%)					**<.0001**
Bone marrow	366 (9)	206 (12)	144 (7)	16 (9)	
PB	3553 (91)	1566 (88)	1823 (93)	164 (91)	
Conditioning intensity, n (%)					**<.0001**
RIC	2681 (69)	1,033 (59)	1500 (77)	148 (82)	
MAC	1179 (31)	707 (41)	440 (23)	32 (18)	
TBI-based conditioning					**<.0001**
No	2901 (75)	1234 (70)	1530 (78)	137 (76)	
Yes	991 (25)	527 (30)	421 (22)	43 (24)	
In vivo TCD with ATG, n (%)					**<.0001**
No	3065 (78)	1459 (82)	1484 (75)	122 (68)	
Yes	854 (22)	313 (18)	483 (25)	58 (32)	
In vivo TCD with lemtuzumab, n (%)					**<.0001**
No	3366 (78)	1528 (86)	1673 (85)	165 (92)	
Yes	553 (14)	244 (14)	294 (15)	15 (8)	
Follow-up of alive patients, mo, median (IQR)	60 (32-90)	64 (30-74)	49 (28-91)	72 (50-109)	.728

ATG indicates antithymocyte globulin.
Significant *P* values are in bold type.

alloHCT, conditioning intensity (RIC/MAC), TBI in the conditioning regimen, graft source (bone marrow versus PB), and TCD, confirmed older age as a significant predictor for NRM but not for RI, resulting in a 3-year IPW-adjusted OS of 62% (60% to 65%) for the young group, 53% (51% to 55%) for the MA group, and 41% (34% to 49%) for the O group ($P < .01$) (Figure 2). Other independent significant predictors of NRM were chemorefractory disease, use of an unrelated donor, no antithymocyte globulin use, and use of an MAC regimen. For the other endpoints, the following variables retained significance for an unfavorable outcome in the Cox models: for age 51 to 65 years, diagnosis of DLBCL, chemorefractory disease, and alemtuzumab TCD for RI: for age category, diagnosis of DLBCL, chemorefractory disease, unrelated donor, PB as cell source, alemtuzumab TCD, MAC regimen, and increasing time from diagnosis to alloHCT for PFS; and for age category, diagnosis of DLBCL, chemorefractory disease, unrelated donor, MAC regimen, and increased interval from diagnosis to alloHCT for OS (Table 2).

Subset Analysis of Patients with Comorbidity Information Available

Comorbidity information by the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) score was available for 979 patients (Y, n = 417; MA, n = 511; O, n = 51). The distributions of baseline and transplantation characteristics of these patients across the 3 age groups were largely similar to that in the entire sample. As expected, comorbidities were more prevalent in the older age groups (Table 3). The 3-year NRM for patients with comorbidity information was 15% (12% to 20%) in the Y group, 27% (23% to 32%) in the MA group, and 45% (26% to 62%) in the O group, similar to that in the entire sample. Accordingly, the risk of relapse (Y, 30% [25% to 35%]; MA, 33% [28% to 37%]; O, 32% [17% to 48%]), PFS (Y, 55% [49% to 61%]; MA, 40% [35% to 45%]; O, 23% [11% to 46%]), and OS (Y, 66% [62% to 72%]; MA, 54% [50% to 59%]; O, 32% [21% to 49%]) at 3 years were in line with the outcomes for the entire sample, indicating that the patients with available comorbidity information were a representative selection.

When including the HCT-CI (0 versus 1 to 2 versus >2) in the multivariate models, the main effects remained unchanged; NRM, PFS, and OS decreased significantly with increasing age (Table 4). In addition, HCT-CI score >0 emerged as an independent adverse predictor of NRM, PFS, and OS, although this was not statistically significant for HCT-CI scores >2.

DISCUSSION

This study, performed in a large sample size from a recent period, identifies older age as an independent risk factor for NRM but not for relapse after alloHCT for NHL. NRM is particularly increased beyond age 65 years (33% at 1 year compared with 20% at 51 to 65 years), resulting in an unadjusted OS disadvantage of the same magnitude (3-year OS, 32% in patients age >65 years versus 49% in those age 51 to 65 years).

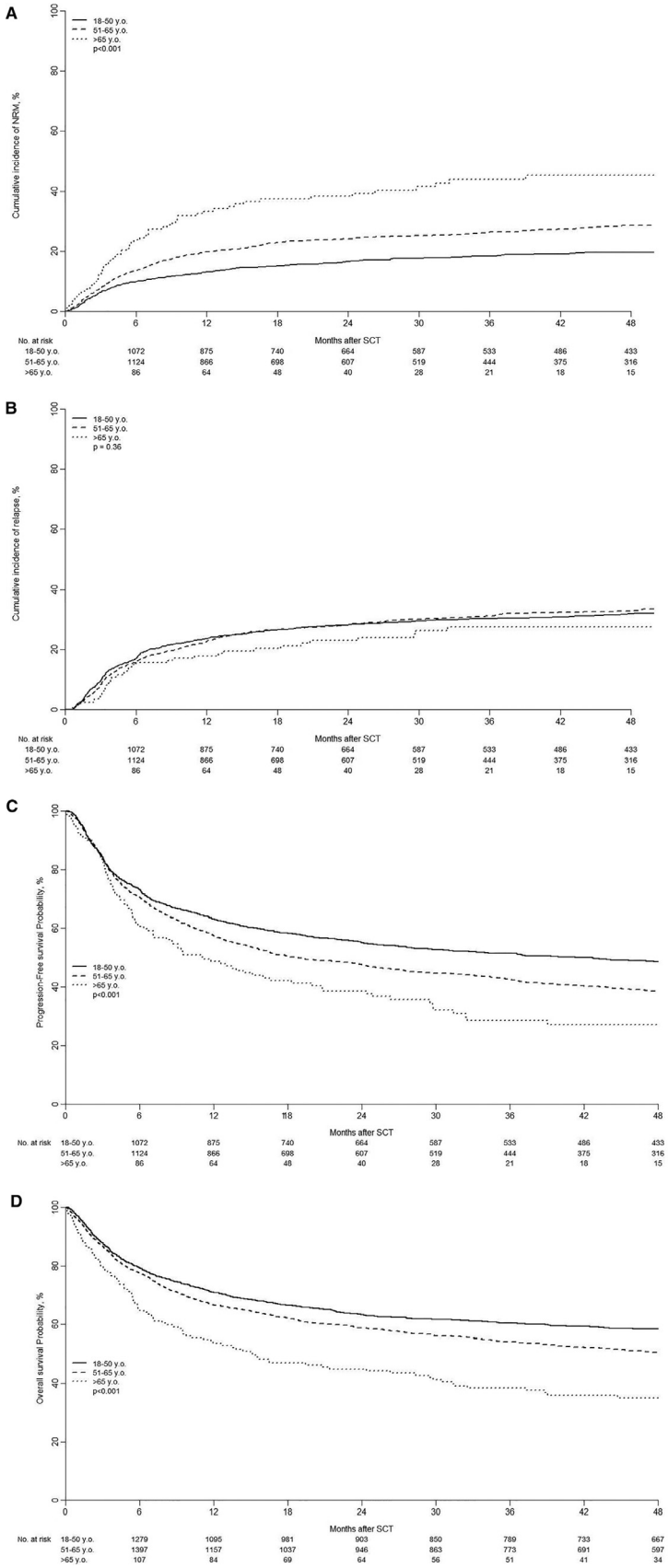

Figure 1. NRM (A), RI (B), PFS (C), and OS (D) by age group.

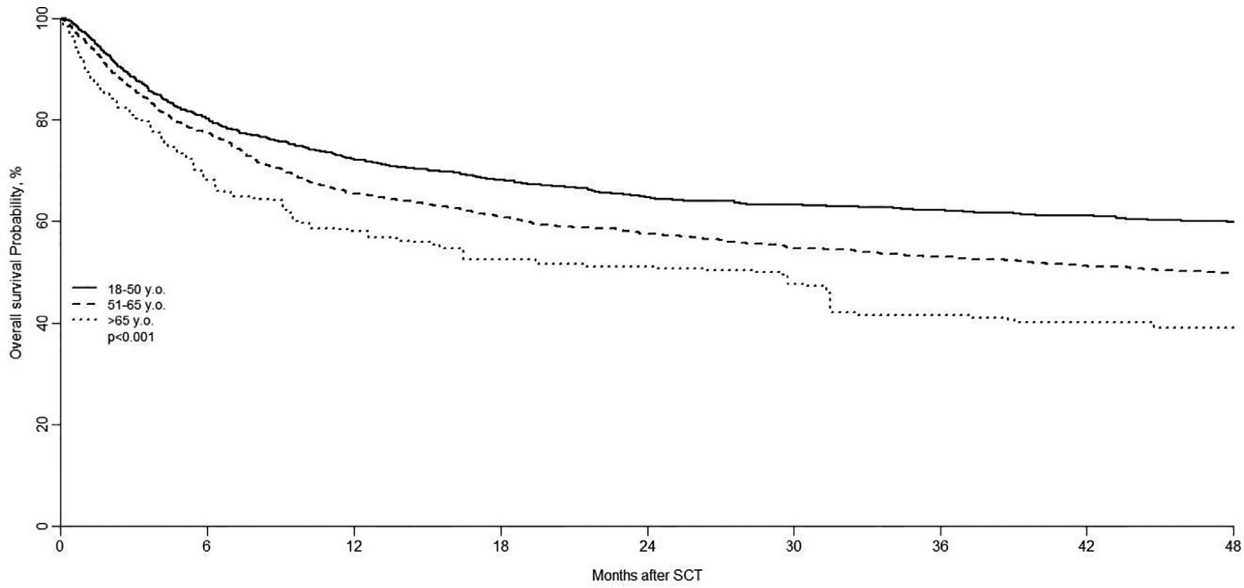

Figure 2. IPW-adjusted OS.

Table 2
Multivariate Analysis of Predictors for Survival Endpoints, All Patients (N = 3919)

Predictor		OS, HR (95% CI); *P* Value	PFS, HR (95% CI); *P* Value	NRM, HR (95% CI); *P* Value	RI, HR (95% CI); *P* Value
Age (reference, 18-50 yr)	51-65 yr	1.34 (1.21-1.49); <.001	1.33 (1.20-1.47); <.001	1.57 (1.35-1.83); <.001	1.17 (1.02-1.34); .021
(Main effect)	>65 yr	1.94 (1.58-2.39); <.001	1.66 (1.34-2.06); <.001	2.56 (1.93-3.40); <.001	1.05 (.74-1.48); .80
Diagnosis (reference, DLBCL)	FL	.51 (.45-.57); <.001	.50 (.44-.56); <.001	.74 (.62-.88); <.001	.37 (.31-.43); <.001
	MCL	.70 (.62-.80); <.001	.76 (.67-.86); <.001	.96 (.79-1.16); .66	.65 (.55-.77); <.001
	PTCL	.80 (.68-.94); .006	.87 (.74-1.01); .072	1.16 (.91-1.48); .23	.70 (.57-.86); <.001
Disease status (reference, chemorefractory)	Chemosensitive	.42 (.38-.48); <.001	.43 (.38-.48); <.001	.54 (.45-.65); <.001	.36 (.31-.42); <.001
Donor type (reference, identical sibling)	Unrelated donor	1.26 (1.13-1.40); <.001	1.23 (1.11-1.37); <.001	1.60 (1.37-1.87); <.001	.98 (.85-1.14); .83
Conditioning (reference, RIC)	MAC	1.29 (1.16-1.44); <.001	1.23 (1.11-1.37); <.001	1.29 (1.09-1.51); .002	1.18 (1.03-1.36); .019
TCD: ATG (reference, no)	Yes	.92 (.81-1.29); .20	.95 (.84-1.07); .40	.79 (.66-.94); .009	1.12 (.95-1.31); .19
TCD: alemtuzumab (reference, no)	Yes	1.12 (.98-1.04); .11	1.19 (1.05-1.36); .007	.90 (.73-1.10); .29	1.49 (1.26-1.77); <.001
Time from diagnosis to alloHCT	Per month increase	1 (1-1); .009	1 (1-1); .36	1 (1-1); <.001	1 (1-1); .36
Graft source (reference, bone marrow)	PB	1.10 (.94-1.30); .24	1.19 (.95-1.50); .13	1.14 (.90-1.45); .27	1.19 (.95-1.50); .13

HR indicates hazard ratio; CI, confidence interval.
Nonsignificant variables considered in the models but not shown in the table: donor-recipient sex constellation, TBI-based conditioning.

Although the difference becomes smaller after multivariate adjustment by IPW including comorbidity, it is obvious that old age as defined here needs to be considered in the decision making for alloHCT in patients with NHL. In contrast, the 20% 1-year NRM in patients age 51 to 65 years exceeded that in patients age <50 years only slightly and is at least comparable to that of favorable patients from a more recent period used to build the EBMT risk score [16], suggesting that age per se should have a limited impact on the indication for alloHCT for NHL in patients up to age 65 years. Although for common alloHCT indications, such as acute myelogenous leukemia and myelodysplastic syndromes, there is a body of literature on alloHCT in elderly patients (with reported NRM risks beyond 65 years largely comparable to those observed in the present study) [17-21], published evidence on this issue in lymphoma is scanty. The sole study explicitly addressing this question was performed by the CIBMTR, investigating 1248 patients age >40 years who underwent alloHCT for NHL between 2001 and 2007, including 82 patients age ≥65 years [15]. Similar to the present analysis, increasing age was identified as a significant adverse factor for NRM, PFS, and OS, but not for RI. For patients age 55 to 64 and >64, 1-year NRM was 27% and 34%, respectively, and 3-year OS was 40% and 39%, respectively. Thus, NRM and survival in the CIBMTR patients age >64 years were comparable to those in our O group, whereas those outcomes in the CIBMTR age 55 to 64 year cohort appeared to be inferior to those in our MA group. Although these findings may suggest improvements in alloHCT safety over time, imbalances in baseline characteristics between the 2 studies and more effective rescue strategies for post-HCT relapse also could have contributed to the superior outcome in our present series.

Apart from the larger sample size and the more recent time, another unique feature of our study is the availability of comorbidity information for a subset of the patients. According to the results obtained here and in line with previous findings from cross-entity studies [22], the presence of comorbidities is a significant risk factor for NRM and survival, but this does not fully explain the outcome disadvantages in our O group.

Table 3
Patient Characteristics by Age Category, Patients with Comorbidity Information Only

Characteristic	Y Group (18-50 yr) (N = 417)	MA Group (51-65 yr) (N = 511)	O Group (>65 yr) (N = 51)	*P* Value
Age at alloHCT, yr, median (IQR)	43 (37-47)	56 (53-59)	67 (66-68)	—
Male sex, n (%)	261 (63)	346 (68)	36 (71)	.20
Diagnosis, n (%)				**<.0001**
DLBCL	150 (36)	142 (28)	17 (33)	
FL	153 (37)	173 (34)	10 (20)	
MCL	38 (9)	150 (29)	719 (37)	
PTCL	76 (18)	46 (9)	13 (10)	
Time from diagnosis to alloHCT, mo, median (IQR)	24 (12-49)	36 (18-62)	36 (20-69)	**<.0001**
Previous autologous HCT, n (%)	183 (44)	253 (50)	32 (63)	**.021**
Disease status at alloHCT, n (%)				**.0029**
Chemosensitive	355 (85)	467 (91)	41 (80)	
Chemorefractory	62 (15)	44 (9)	10 (20)	
Karnofsky Performance Score, n (%)				.41
Good (≥80)	359 (86)	453 (89)	44 (86)	
Poor (<80)	29 (7)	22 (4)	2 (3.9)	
Unknown	29 (7)	36 (7)	5 (9.8)	
Donor, n (%)				**<.0001**
Identical sibling	274 (66)	313 (61)	16 (31)	
Unrelated	143 (34)	198 (39)	35 (68)	
Graft source, n (%)				.46
Bone marrow	35 (8)	32 (6)	3 (6)	
PB	382 (92)	497 (94)	48 (94)	
Conditioning intensity, n (%)				**<.0001**
RIC	253 (61)	420 (82)	49 (96)	
MAC	160 (38)	89 (17)	15 (29)	
Unknown	4 (1)	2 (0.5)	0	
TBI-based conditioning, n (%)				**.0032**
No	309 (74)	419 (82)	36 (71)	
Yes	106 (25)	87 (17)	15 (29)	
Unknown	2 (0.5)	5 (1)	0	
In vivo TCD (ATG), n (%)				**.023**
No	328 (79)	364 (71)	35 (69)	
Yes	89 (21)	147 (29)	16 (31)	
In vivo TCD (alemtuzumab), n (%)				.29
No	309 (74)	360 (70)	40 (78)	
Yes	108 (26)	151 (30)	11 (22)	
HCT-CI score, n (%)				**.042**
0	286 (69)	307 (60)	28 (55)	
1-2	55 (13)	114 (22)	12 (24)	
>2	56 (13)	63 (12)	8 (16)	
Unknown*	20 (5)	27 (5)	3 (6)	
Follow-up of alive patients, yr, median (IQR)	4.0 (1.2-6.0)	3.9 (2.0-5.4)	3.0 (0.7-4.0)	.16

Significant *P* values are in bold type.
* Ticked "comorbidity yes" on the MED-A without giving HCT-CI details.

Although the strengths of our present study (ie, large sample size, recent time frame, and comorbidity information considered) are obvious, there are some limitation, including its retrospective design and the still-limited number of patients age ≥65 years. Nevertheless, it may be concluded from our data that age is not a major confounder of alloHCT outcomes in patients with NHL up age 65 years. Beyond that age, alloHCT is still feasible and effective, but the increasing risk of NRM must be considered when determining the indication for alloHCT to treat NHL.

NHL is predominantly a disease of the elderly, and the prognosis of relapsed or refractory disease remains dismal and the

Table 4
Multivariate Analysis of Predictors for Survival Endpoints, Patients with Comorbidity Information Only (N = 979)

Predictor		OS, HR (95% CI); *P* value	PFS, HR (95% CI); *P* Value	NRM, HR (95% CI); *P* Value	RI, HR (95% CI); *P* Value
Age (reference, 18-50 yr)	51-65 yr	1.50 (1.18-1.90); <.001	1.43 (1.14-1.79); .0019	1.61 (1.12-2.32); .0097	1.33 (.99-1.77); .055
(Main effect)	>65 yr	2.44 (1.58-3.76); <.001	1.65 (1.33-2.05) <.001	2.19 (1.15-4.14); .016	1.55 (.82-2.92); .18
Diagnosis (reference, DLBCL)	FL	.52 (.39-.69); <.001	.59 (.46-.77); <.001	.62 (.41-.93); .023	.58 (.42-.82); .0016
	MCL	.76 (.57-1); .049	.93 (.72-1.22); .61	1.11 (.74-1.66); .61	.82 (.58-1.17); .27
	PTCL	.74 (.53-1.05); .089	.85 (.61-1.18); .33	.86 (.50-1.48); .58	.83 (.55-1.26); .39
Disease status (reference, chemorefractory)	Chemosensitive	.43 (.33-.57); <.001	.46 (.35-.61); <.001	.57 (.36-.91); .018	.40 (.29-.57); <.001
Donor type (reference, identical sibling)	UD	1.17 (.92-1.49); .21	1.22 (.97-1.53); .087	1.72 (1.22-2.43); .0022	.95 (.70-1.29); .75
Conditioning (reference, RIC)	MAC	1.39 (1.09-1.79); .0086	1.25 (.98-1.59); .067	1.28 (.87-1.88); .21	1.24 (.91-1.69); .17
HCT-CI score (reference, 0)	1-2	1.53 (1.20-1.97); <.001	1.30 (1.02-1.66); .033	1.69 (1.17-2.43); .0049	1.09 (.78-1.51); .63
	>2	1.27 (.92-1.76); .14	1.06 (.77-1.45); .73	1.43 (.89-2.28); .14	.85 (.56-1.31); .47

Nonsignificant variables considered in the models but not shown in the table: time from diagnosis to alloHCT, donor-recipient sex constellation, TBI-based conditioning, graft source, TCD.

management of these patients remains challenging [23-27]. The information provided in this cohort of patients with NHL, the largest reported to date, is useful and relevant, especially in the era of evolving therapies. There are multiple novel agents that can be used as bridging therapies to alloHCT in high-risk groups of elderly patients. The development of new conditioning regimens and the use of alternate alloHCT donors [28-30] provides NHL patients eligible for alloHCT with more treatment options not limited by their age. The data from this retrospective study are even more relevant now with the availability of treatment with autologous chimeric antigen receptor (CAR) T cells [31-39] and donor-derived CAR T [40-42] or the administration of CAR T cells after relapse post-alloHCT [39, 43-45].

ACKNOWLEDGMENTS

Presented in part in abstract form at the 42nd Annual Meeting of the European Society for Blood and Marrow Transplantation, Valencia, Spain, April 2, 2016.

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: The authors have no conflicts of interest to report.

REFERENCES

1. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood*. 2010;116:3724–3734.
2. van Kampen RJ, Canals C, Schouten HC, et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell transplantation: an analysis of the European Group for Blood and Marrow Transplantation Registry. *J Clin Oncol*. 2011;29:1342–1348.
3. Glass B, Hasenkamp J, Wulf G, et al. Rituximab after lymphoma-directed conditioning and allogeneic stem-cell transplantation for relapsed and refractory aggressive non-Hodgkin lymphoma (DSHNHL R3): an open-label, randomised, phase 2 trial. *Lancet Oncol*. 2014;15:757–766.
4. Fenske TS, Ahn KW, Graff TM, et al. Allogeneic transplantation provides durable remission in a subset of DLBCL patients relapsing after autologous transplantation. *Br J Haematol*. 2016;174:235–248.
5. Robinson SP, Boumendil A, Finel H, et al. Reduced-intensity allogeneic stem cell transplantation for follicular lymphoma relapsing after an autologous transplant achieves durable long-term disease control: An analysis from the Lymphoma Working Party of the EBMT [e-pub ahead of print]. *Ann Oncol* 2016; pii: mdw124, accessed Mar 8.
6. Heinzelmann F, Bethge W, Beelen DW, et al. Allogeneic hematopoietic cell transplantation as curative therapy for non-transformed follicular lymphomas. *Bone Marrow Transplant*. 2016;51:654–662.
7. Fenske TS, Zhang MJ, Carreras J, et al. Autologous or reduced-intensity conditioning allogeneic hematopoietic cell transplantation for chemotherapy-sensitive mantle-cell lymphoma: analysis of transplantation timing and modality. *J Clin Oncol*. 2014;32:273–281.
8. Montoto S, Corradini P, Dreyling M, et al. Indications for hematopoietic stem cell transplantation in patients with follicular lymphoma: a consensus project of the EBMT-Lymphoma Working Party. *Haematologica*. 2013;98:1014–1021.
9. Corradini P, Vitolo U, Rambaldi A, et al. Intensified chemo-immunotherapy with or without stem cell transplantation in newly diagnosed patients with peripheral T-cell lymphoma. *Leukemia*. 2014;28:1885–1891.
10. Smith SM, Burns LJ, van Besien K, et al. Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. *J Clin Oncol*. 2013;31:3100–3109.
11. Robinson S, Dreger P, Caballero D, et al. The EBMT/EMCL consensus project on the role of autologous and allogeneic stem cell transplantation in mantle cell lymphoma. *Leukemia*. 2015;29:464–473.
12. Sureda A, Bader P, Cesaro S, et al. Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2015. *Bone Marrow Transplant*. 2015;50:1037–1056.
13. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2015;21:1863–1869.
14. Fenske TS, Hamadani M, Cohen JB, et al. Allogeneic hematopoietic cell transplantation as curative therapy for patients with non-Hodgkin lymphoma: increasingly successful application to older patients. *Biol Blood Marrow Transplant*. 2016;22:1543–1551.
15. McClune BL, Ahn KW, Wang HL, et al. Allotransplantation for patients age ≥40 years with non-Hodgkin lymphoma: encouraging progression-free survival. *Biol Blood Marrow Transplant*. 2014;20:960–968.
16. Gratwohl A, Stern M, Brand R, et al. Risk score for outcome after allogeneic hematopoietic stem cell transplantation: a retrospective analysis. *Cancer*. 2009;115:4715–4726.
17. Lim Z, Brand R, Martino R, et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. *J Clin Oncol*. 2010;28:405–411.
18. Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. *JAMA*. 2011;306:1874–1883.
19. Farag SS, Maharry K, Zhang MJ, et al. Comparison of reduced-intensity hematopoietic cell transplantation with chemotherapy in patients age 60-70 years with acute myelogenous leukemia in first remission. *Biol Blood Marrow Transplant*. 2011;17:1796–1803.
20. Heidenreich S, Ziagkos D, de Wreede LC, et al. Allogeneic stem cell transplantation for patients age ≥70 years with myelodysplastic syndrome: a retrospective study of the MDS Subcommittee of the Chronic Malignancies Working Party of the EBMT. *Biol Blood Marrow Transplant*. 2017;23:44–52.
21. Pohlen M, Groth C, Sauer T, et al. Outcome of allogeneic stem cell transplantation for AML and myelodysplastic syndrome in elderly patients (≥60 years). *Bone Marrow Transplant*. 2016;51:1441–1448.
22. Sorror ML, Storb RF, Sandmaier BM, et al. Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2014;32:3249–3256.
23. Glass B, Dohm AJ, Truemper LH, et al. Refractory or relapsed aggressive B-cell lymphoma failing (R)-CHOP: an analysis of patients treated on the RICOVER-60 trial. *Ann Oncol*. 2017;28:3058–3064.
24. Morgensztern D, Walker GR, Koniaris LG, Lossos IS. Lack of survival improvement in patients with peripheral T-cell lymphoma: a Surveillance, Epidemiology, and End Results analysis. *Leuk Lymphoma*. 2011;52:194–204.
25. Pulte D, Gondos A, Brenner H. Expected long-term survival of older patients diagnosed with non-Hodgkin lymphoma in 2008-2012. *Cancer Epidemiol*. 2012;36:e19–e25.
26. Pulte D, Jansen L, Castro FA, Brenner H. Changes in the survival of older patients with hematologic malignancies in the early 21st century. *Cancer*. 2016;122:2031–2040.
27. Crozier JA, Sher T, Yang D, et al. Persistent disparities among patients with T-cell non-Hodgkin lymphomas and B-cell diffuse large cell lymphomas over 40 years: A SEER database review. *Clin Lymphoma Myeloma Leuk*. 2015;15:578–585.
28. Kanate AS, Mussetti A, Kharfan-Dabaja MA, et al. Reduced-intensity transplantation for lymphomas using haploidentical related donors vs HLA-matched unrelated donors. *Blood*. 2016;127:938–947.
29. Passweg JR, Baldomero H, Bader P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. *Bone Marrow Transplant*. 2016;51:786–792.
30. Dietrich S, Finel H, Martinez C, et al. Post-transplant cyclophosphamide-based haplo-identical transplantation as alternative to matched sibling or unrelated donor transplantation for non-Hodgkin lymphoma: a registry study by the European society for blood and marrow transplantation. *Leukemia*. 2016;30:2086–2089.
31. Brudno JN, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for lymphoma. *Nat Rev Clin Oncol*. 2018;15:31–46.
32. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol*. 2015;33:540–549.
33. Kochenderfer JN, Somerville RPT, Lu T, et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. *J Clin Oncol*. 2017;35:1803–1813.
34. Kochenderfer JN, Somerville RPT, Lu T, et al. Long-duration complete remissions of diffuse large B cell lymphoma after anti-CD19 chimeric antigen receptor T cell therapy. *Mol Ther*. 2017;25:2245–2253.
35. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med*. 2017;377:2545–2554.
36. Rosenbaum L. Tragedy, perseverance, and chance—the story of CAR-T therapy. *N Engl J Med*. 2017;377:1313–1315.
37. Chen KH, Wada M, Pinz KG, et al. Preclinical targeting of aggressive T-cell malignancies using anti-CD5 chimeric antigen receptor. *Leukemia*. 2017;31:2151–2160.
38. Pinz K, Liu H, Golightly M, et al. Preclinical targeting of human T-cell malignancies using CD4-specific chimeric antigen receptor (CAR)-engineered T cells. *Leukemia*. 2016;30:701–707.
39. Jain MD, Davila ML. Concise review: emerging principles from the clinical application of chimeric antigen receptor T cell therapies for B cell malignancies. *Stem Cells*. 2018;36:36–44.
40. Rapoport AP. Donating used CARs. *Blood*. 2013;122:4007–4009.

41. Ghosh A, Smith M, James SE, et al. Donor CD19 CAR T cells exert potent graft-versus-lymphoma activity with diminished graft-versus-host activity. *Nat Med*. 2017;23:242–249.
42. Brudno JN, Somerville RP, Shi V, et al. Allogeneic T cells that express an anti-CD19 chimeric antigen receptor induce remissions of B-cell malignancies that progress after allogeneic hematopoietic stem-cell transplantation without causing graft-versus-host disease. *J Clin Oncol*. 2016;34:1112–1121.
43. Smith M, Zakrzewski J, James S, Sadelain M. Posttransplant chimeric antigen receptor therapy. *Blood*. 2018;131:1045–1052.
44. Cruz CR, Micklethwaite KP, Savoldo B, et al. Infusion of donor-derived CD19-redirected virus-specific T cells for B-cell malignancies relapsed after allogeneic stem cell transplant: a phase 1 study. *Blood*. 2013;122:2965–2973.
45. Kochenderfer JN, Dudley ME, Carpenter RO, et al. Donor-derived CD19-targeted T cells cause regression of malignancy persisting after allogeneic hematopoietic stem cell transplantation. *Blood*. 2013;122:4129–4139.