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REPORT

Influence of Age and Histology on Outcome in Adult Non-Hodgkin Lymphoma Patients Undergoing Autologous Hematopoietic Cell Transplantation (HCT): A Report from The Center For International Blood & Marrow Transplant Research (CIBMTR)

Hillard M. Lazarus,[1] Jeanette Carreras,[2] Christian Boudreau,[3] Fausto R. Loberiza, Jr.,[4] James O. Armitage,[4] Brian J. Bolwell,[5] César O. Freytes,[6] Robert Peter Gale,[7] John Gibson,[8] Gregory A. Hale,[9] David J. Inwards,[10] Charles F. LeMaistre,[11] Dipnarine Maharaj,[12] David I. Marks,[13] Alan M. Miller,[14] Santiago Pavlovsky,[15] Harry C. Schouten,[16] Koen van Besien,[17] Julie M. Vose,[4] Jacob D. Bitran,[18] Issa F. Khouri,[19] Philip L. McCarthy,[20] Hongmei Yu,[21] Philip Rowlings,[22] Derek S. Serna,[2] Mary M. Horowitz,[2] J. Douglas Rizzo[2]

To compare the clinical outcomes of older (age ≥55 years) non-Hodgkin lymphoma (NHL) patients with younger NHL patients (<55 years) receiving autologous hematopoietic cell transplantation (HCT) while adjusting for patient-, disease-, and treatment-related variables, we compared autologous HCT outcomes in 805 NHL patients aged ≥55 years to 1949 NHL patients <55 years during the years 1990–2000 using data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). In multivariate analysis, older patients with aggressive histologies were 1.86 times (95% confidence interval [CI] 1.43-2.43, $P < .001$) more likely than younger patients to experience treatment-related mortality (TRM). Relative death risks were 1.33 times (CI 1.04-1.71, $P = .024$) and 1.50 times (CI 1.33-16.9, $P < .001$) higher in older compared to younger patients with follicular grade I/II and aggressive histologies, respectively. Autologous HCT in older NHL patients is feasible, but most disease-related outcomes are statistically inferior to younger patients. Studies addressing supportive care particular to older patients, who are most likely to benefit from this approach, are recommended.

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KEY WORDS: Non-Hodgkin lymphoma, Autologous HCT, Relapse, Second complete remission, Elderly

INTRODUCTION

In the United States, over 55,000 non-Hodgkin lymphoma (NHL) patients are diagnosed each year, and the majority of the patients are over 55 years of age; furthermore, incidence rates have risen with each year of age above 55 years, with the rate of increase larger among each successively older age group

From the [1]University Hospitals Case Medical Center, Cleveland, Ohio; [2]Lymphoma Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR), Medical College of Wisconsin, Milwaukee, Wisconsin; [3]University of Waterloo, Waterloo, Ontario, Canada; [4]University of Nebraska Medical Center, Omaha, Nebraska; [5]Cleveland Clinic Foundation, Cleveland, Ohio; [6]University of Texas Health Science Center, San Antonio, Texas; [7]Center for Advanced Studies in Leukemia, Los Angeles, Californai; [8]Royal Prince Alfred Hospital, Camperdown, Australia; [9]St. Jude Children Research Center, Memphis, Tennessee; [10]Mayo Clinic, Rochester, Minnesota; [11]Texas Transplant Institute, San Antonio, Texas; [12]South Florida Bone Marrow Stem Cell Institute, Boynton Beach, Florida; [13]Bristol Children's Hospital, Bristol, United Kingdom; [14]Tulane University Medical Center, New Orleans, Louisiana; [15]Fundaleu, Buenos Aires, Argentina; [16]University Hospitals Maastricht, Maastricht, The Netherlands; [17]University of Chicago, Chicago, Illinois; [18]Advocate Lutheran General Hospital, Park Ridge, Illinois; [19]MD Anderson Cancer Research Center, Houston, Texas; [20]Roswell Park Cancer Institute, Buffalo, New York; [21]Shanxi Medical University, People's Republic of China; and [22]Newcastile Mater Hospital, Waratah, Australia.

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Correspondence and reprint requests: Hillard M. Lazarus, MD, Department of Medicine, University Hospitals Case Medical Center, 11100 Euclid Avenue, Cleveland, OH 44106 (e-mail: hillard.lazarus@case.edu).

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[1,2]. Older age is a well-recognized poor prognostic factor [3,4]. Reluctance to offer autologous hematopoietic cell transplantation (HCT) to older patients with hematologic malignancies is reinforced by a high treatment-related mortality (TRM). Several studies published more than a decade ago showed a direct correlation with increased age and higher likelihood for hepatic veno-occlusive disease (VOD), interstitial pneumonitis, and other fatal complications [5,6]. Additionally, Weaver et al. [7] reported a large study of community cancer center patients receiving autologous HCT, for various malignant disorders where 9.5% of patients >60 years died of treatment-related causes within 100 days of HCT compared with 3% of younger patients. It is unclear what selection criteria were used when considering HCT in the elderly population included in this study. The median age of autologous HCT in several recent series is 35 to 45 years [6,8-12].

We performed a multicenter retrospective study using an observational database to determine the effect of age (ie, <55 years versus ≥55 years old) on the short-term and long-term outcomes of NHL patients who have undergone an autologous HCT. Although the literature commonly reports age 60 years as a cut-off, in part reflecting the prognostic index derived from a nontransplant data set [3], we chose 55 years as the optimal value to demonstrate the largest differences for individuals from 2 age groups (vide infra). Further, some reports for NHL HCT procedures combine results for indolent and aggressive histologies. Our main study objective was to compare overall survival (OS), disease-free survival (DFS), TRM, and relapse rates between younger and older patients, for patients with indolent (follicular center cell grade I and II) and aggressive lymphoma (follicular III, diffuse large cell, and immunoblastic). We also sought to identify patient-, disease-, and treatment-related factors correlated with outcome. These data will provide important information for treatment decisions for NHL patients being considered for autologous HCT.

PATIENTS AND METHODS

Center for International Blood and Marrow Transplant Research (CIBMTR)

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR), Autologous Blood and Marrow Transplant Registry (ABMTR), and the National Marrow Donor Program (NMDP), which comprises a voluntary working group of more than 450 transplant centers worldwide that contribute detailed data on consecutive allogeneic and autologous transplants to a Statistical Center at the Health Policy Institute of the Medical College of Wisconsin in Milwaukee or the NMDP Coordinating Center in Minneapolis. Participating centers are required to report all consecutive transplants; compliance is monitored by on-site audits. Subjects are followed longitudinally, with yearly follow-up. Computerized checks for errors, physicians' review of submitted data and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are done with a waiver of informed consent, and in compliance with HIPAA regulations, as determined by the institutional review board and the Privacy Officer of the Medical College of Wisconsin.

The CIBMTR collects data at 2 levels: registration and research. Registration data include disease type, age, sex, pretransplant disease stage and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow- and/or blood-derived stem cells), high-dose conditioning regimen, posttransplant disease progression and survival, development of a new malignancy, and cause of death. Requests for data on progression or death for registered patients are at 6-month intervals. All CIBMTR teams contribute Registration data. Research data are collected on a subset of registered patients selected using a weighted randomization scheme and include detailed disease, and pre- and post-transplant clinical information. Based on data collected in the Centers for Disease Control Hospital Surveys [13,14] and the U.S. Government Accounting Office [15,16] and worldwide surveys of transplant activity, approximately 40% of allogeneic transplants worldwide and more than 50% of autologous HCTs in North and South America are registered with the CIBMTR.

Patients

Between January 1, 1990, and December 31, 2000, 8244 NHL (histology limited to indolent and aggressive) patients who received autologous HCT were registered with the CIBMTR. Of these, a total of 2754 (33%) NHL patients have complete research data and were included in the study. Forty-eight patients were excluded because they were younger than 18 years prior to transplantation. A total of 1949 patients were less than age 55 years at time of transplantation, whereas 805 were at least 55 years old. Patients were reported to the CIBMTR by 176 centers in 10 different countries. To assure that the research patients were representative of all registered patients, demographics, relapse, and survival rates between research and registered patients were compared; no differences were noted. Median follow-up of survivors after autologous HCT was 92 months (range: <1-198 months) for patients <55 years and 83 months (range: 2-196 months) for patients ≥55 years.

Study Endpoints

Primary outcomes studied were TRM, relapse, treatment failure (inverse of DFS), and OS. TRM was

Table 1. Characteristics of NHL Patients Undergoing Autologous HCT from 1990 to 2000 and Reported to the CIBMTR

	Follicular Grade I/II		Follicular Grade III DLBCL Immunoblastic NHL		
	<55 Years	≥55 Years	<55 Years	≥55 Years	
Variable	N (%)	N (%)	N (%)	N (%)	*P*-Value*
Number of patients	615	173	1334	632	
Age, median (range), years	46 (19-55)	60 (55-72)	44 (18-55)	61 (55-73)	
Male sex	339 (55)	105 (61)	776 (58)	367 (58)	.48
Karnofsky performance score at transplant					<.001
<90	145 (25)	41 (24)	475 (37)	237 (38)	
≥90	440 (75)	132 (76)	819 (63)	381 (62)	
Missing	*30*	*0*	*40*	*14*	
Disease stage at diagnosis					<.001
I or II	87 (14)	41 (24)	479 (36)	221 (35)	
III or IV	520 (85)	129 (74)	822 (62)	402 (64)	
Unknown	8 (1)	3 (2)	33 (2)	9 (1)	
B symptoms at diagnosis					<.001
Absent	383 (62)	112 (65)	691 (52)	362 (57)	
Present	193 (32)	39 (22)	552 (41)	211 (34)	
Unknown	39 (6)	22 (13)	91 (7)	59 (9)	
Disease status at transplant					<.001
CR1	87 (16)	14 (9)	178 (15)	50 (8)	
CR2+	98 (18)	31 (21)	217 (18)	113 (19)	
PIF-sensitive	118 (21)	27 (18)	236 (19)	69 (12)	
PIF-resistant	18 (3)	4 (3)	78 (6)	22 (4)	
PIF-untreated/unknown	10 (2)	0	13 (1)	3 (1)	
REL-sensitive	165 (30)	53 (35)	343 (28)	243 (42)	
REL-resistant	30 (5)	17 (11)	102 (9)	57 (10)	
REL-untreated/unknown	28 (5)	4 (3)	53 (4)	25 (4)	
Missing	*61*	*23*	*114*	*50*	
Chemosensitivity at transplant					.01
Sensitivity	479 (78)	137 (79)	976 (73)	498 (79)	
Resistant	56 (9)	22 (13)	184 (14)	74 (12)	
Untreated/not evaluable/unknown	80 (13)	14 (8)	174 (13)	60 (9)	
Interval from diagnosis to transplant					<.001
<12 months	126 (20)	34 (20)	613 (46)	172 (27)	
≥12 months	489 (80)	139 (80)	721 (54)	460 (73)	
Graft type					<.001
Bone marrow	191 (31)	38 (22)	398 (30)	113 (18)	
Peripheral blood	424 (69)	135 (78)	936 (70)	519 (82)	
Use of involved-field radiation	34 (6)	7 (4)	61 (5)	16 (3)	.06
Use of TBI	280 (46)	59 (34)	320 (24)	120 (19)	<.001
Conditioning regimen					<.001
TBI	280 (46)	59 (34)	320 (24)	120 (19)	
Cy+VP16	46 (7)	9 (5)	132 (10)	52 (8)	
BCNU-based: BEAM/BEAC	170 (28)	64 (37)	643 (48)	315 (50)	
Platinum based (no Cy)	24 (4)	10 (6)	64 (5)	29 (5)	
Others	95 (15)	31 (18)	175 (13)	116 (18)	
Year of transplantation					<.001
1990-1994	327 (53)	56 (32)	528 (39)	168 (27)	
1995-1996	130 (21)	44 (25)	334 (25)	165 (26)	
1997-1998	104 (17)	46 (27)	302 (23)	174 (27)	
1999-2000	54 (9)	27 (16)	170 (13)	125 (20)	
In vitro purging performed	142 (23)	34 (20)	99 (7)	45 (7)	<.001
G-CSF or GM-CSF to promote engraftment	450 (73)	129 (75)	1007 (75)	496 (78)	.18
New malignancy					.02
MDS/AML	8 (1)	1 (1)	9 (1)	6 (1)	
Other leukemia	0	0	1 (<1)	0	
Solid tumor	4 (1)	1 (1)	4 (<1)	8 (1)	
Skin cancer	2 (<1)	1 (1)	0	1 (<1)	
New malignancy, not specified	47 (8)	13 (7)	55 (4)	30 (5)	
None	553 (90)	156 (90)	1261 (95)	584 (93)	
Missing	*1*	*1*	*4*	*3*	
Median follow-up of survivors, months	90 (3-180)	81 (2-155)	93 (1-198)	84 (3-196)	

CR indicates complete remission; PIF, primary induction failure; TBI, total body irradiation; Cy, cyclophosphamide; GF, growth factors; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; NHL, non-Hodgkin lymphoma; CIBMTR, Center for International Blood and Marrow Transplant Research.

Follow-up completeness index = 92% (overall); 91% (<55 years); 94% (≥55 years).

*The chi-square test was used for discrete covariates; the Kruskal-Wallis test was used for continuous covariates.

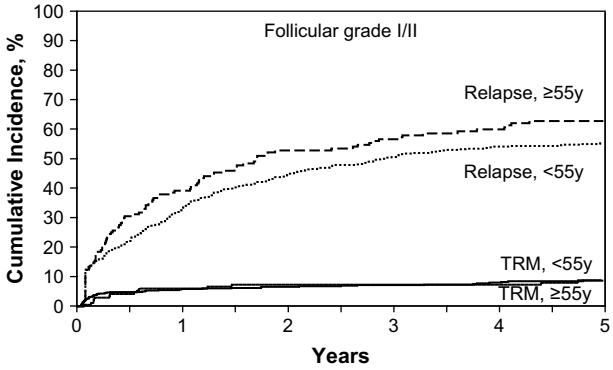

Figure 1. Cumulative incidence of TRM and relapse after autologous HCTs for follicular grade I/II NHL patients aged <55 years versus ≥55 years.

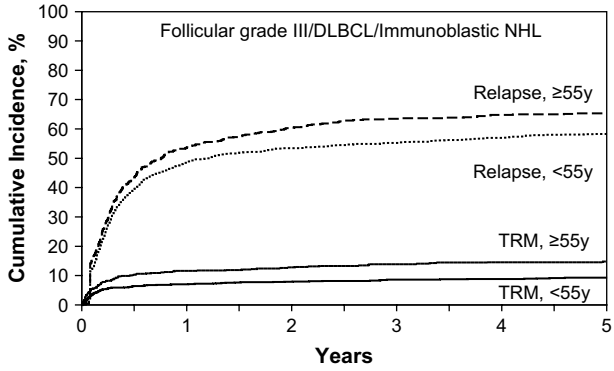

Figure 3. Cumulative incidence of TRM and relapse after autologous HCTs for follicular grade III/diffuse large B cell/immunoblastic NHL patients aged <55 years versus ≥55 years.

defined as death in continuous complete remission (CR) or any death occurring <28 days after transplant. Patients who never achieved CR were considered to relapse at day 28. Patients with recurrent lymphoma were censored for TRM at the time of relapse. Likewise, those alive in remission were censored for relapse at the last follow-up evaluation. For DFS, patients were considered treatment failures at the time of relapse or at the time of death from any cause. Patients alive in continuous complete remission were censored at last follow-up evaluation. OS was defined as the interval between transplant and death from any cause. Surviving patients were censored at the date of last contact.

Statistical Methods

Univariate probabilities of TRM and relapse were computed using cumulative incidence to accommodate competing risks. Univariate probabilities of treatment failure (inverse of DFS) and OS were computed using the Kaplan-Meier estimator [17].

Statistical techniques, that is, Contal and O'Quigley [18] and maximum likelihood theory, were used to determine the optimal categorization of age groups among cut-off points including ages 50, 55, 60, and 65 years. The choice of 55 years produced the optimal age cutoff value based on these statistical methods; optimal in the sense that 55 years maximizes the likelihood function and yields the largest difference between individuals from the 2 age groups (data not shown). Because the literature commonly reports categories based around 60 years of age, we also analyzed the data using age 60 years as the cut-off point. These analyses produced similar results (data not shown). Comparisons of the 2 age groups and assessment of other potential risk factors for outcomes of interest were done using multivariate Cox proportional hazards regression analysis [19]. Age group (≥55 years versus <55 years) was forced into all Cox models. Other variables considered in the analysis included sex, Karnofsky performance score at transplant (<90% versus ≥90%), disease stage at diagnosis (stage I/II versus III/IV), presence versus absence of B symptoms, disease status at transplant, interval from diagnosis to transplant (<12 months versus ≥12 months), type of graft (bone marrow versus peripheral blood), use of involved-field radiation, conditioning regimen (no total body irridiation [TBI] versus TBI), year of transplant, use of purging, and use of granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor

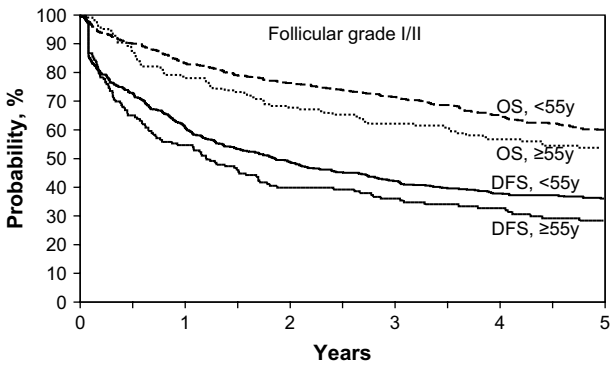

Figure 2. Cumulative incidence of DFS and OS after autologous HCTs for follicular grade I/II NHL patients aged <55 years versus ≥55 years.

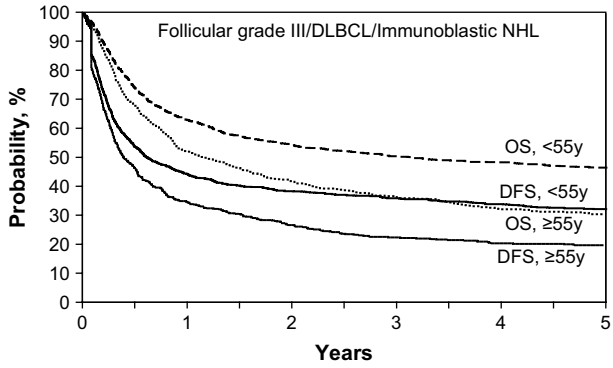

Figure 4. Cumulative incidence of DFS and OS after autologous HCTs for follicular grade III/diffuse large B cell/immunoblastic NHL patients aged <55 years versus ≥55 years.

Table 2A. Multivariate Analysis of Treatment-Related Mortality for Follicular Grade I/II NHL

Variables	N	Relative Risk of TRM (95% CI)	*P*-value
Main effect of age			
<55	595	1.00	.54
≥ 55	168	1.18 (0.69-2.02)	
Other significant covariates			
Type of graft			<.001*
Bone marrow	221	1.00	
Peripheral blood†			
Within first 12 months after transplant	235	0.26 (0.14-0.48)	<.001
Beyond first 12 months after transplant	307	1.26 (0.61-2.60)	.54
Conditioning regimen			
No TBI	434	1.00	.014
TBI	329	1.75 (1.12-2.72)	

TBI indicates total body irridiation; TRM, treatment-related mortality; CI, confidence interval; HCT, hematopoietic cell transplantation, NHL, non-Hodgkin lymphoma.
*Two degrees of freedom test.
†Time-dependent covariates. The effect of peripheral blood graft type on outcome differs with the length of time after transplant. The risk of TRM is lower for recipients of peripheral blood grafts within the first 12 months following HCT compared to bone marrow recipients, but no different in the period beyond 12 months after HCT.

Table 2B. Multivariate Analysis of Treatment-Related Mortality for Follicular Grade III/Diffuse Large B Cell/Immunoblastic NHL

Variables	N	Relative Risk of TRM (95% CI)	*P*-Value
Main effect of age			
<55	1294	1.00	<.001
≥55	615	1.86 (1.43-2.43)	
Other significant covariates			
Karnofsky performance score at transplant*			
(1) ≥90%	1167	1.00	.003†
(2) <90%	692	1.59 (1.20-2.04)	.001
(3) Missing	50	1.04 (0.50-2.17)	.26
Disease status at transplant‡			
(1) CR1	221	1.00	<.001§
(2) PIF-sensitive	293	1.35 (0.77-2.38)	.30
(3) PIF-resistant	98	1.39 (0.61-3.14)	.44
(4) REL-sensitive	570	1.17 (0.69-1.98)	.56
(5) REL-resistant	155	3.35 (1.88-5.95)	<.001
(6) CR2+	324	1.65 (0.96-2.81)	.07
(7) REL-untreated/unknown	75	2.17 (1.07-4.39)	.032
(8) PIF-untreated/unknown	15	4.43 (1.52-12.96)	.007
(9) Unknown	158	1.70 (0.92-3.14)	.09
Time from diagnosis to transplant			
<12 months	759	1.00	.040
≥12 months	1150	1.41 (1.02-1.95)	
Use of purging			
No	1771	1.00	.008
Yes	138	1.77 (1.16-2.68)	
G-CSF or GM-CSF to promote engraftment			
No	449	1.00	.017†
Yes¶			
Within first 8 months after transplant	800	0.69 (0.49-0.98)	.039
Beyond first 8 months after transplant	660	1.70 (0.99-2.92)	.054

CR indicates complete remission; PIF, primary induction failure; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; TRM, treatment-related mortality; NHL, non-Hodgkin lymphoma.
*Other pairwise comparisons: $P_{23} = .91$.
†Two degrees of freedom.
‡Other significant pairwise comparisons: $P_{45} \geq .001$; $P_{48} = .012$; $P_{52} = .001$; $P_{53} = .028$; $P_{56} = .003$; $P_{59} = .019$; $P_{74} = .046$; $P_{82} = .027$.
§Eight degrees of freedom.
¶Time-dependant covariates. The effect of G-CSF or GM-CSF to promote engraftment differs with the length of time after transplant. The risk of TRM is lower for recipients with G-CSF or GM-CSF to promote engraftment within the first 8 months following HCT compared to recipients who did not receive G-CSF or GM-CSF, but no different in the period beyond 8 months after HCT.

(GM-CSF) to promote engraftment (defined as initiation of these therapies within 7 days of HCT).

Overall completeness index follow-up is 92% (<55 = 91%; ≥55 = 94%). To accommodate the physiologic differences between histologies, separate analyses were performed for indolent and aggressive lymphoma histologies. For all outcomes of interest, the assumption of proportional hazards was tested using time-dependent covariates and graphical methods [20]. For relapse and treatment failure, all covariates considered in the multivariate analyses satisfied the proportionality assumption, for both histology types. For OS, nonproportional hazards were identified for Karnofsky performance score at transplant (indolent histology patients) and interval from diagnosis to transplant (aggressive histology patients). Cox regression models for OS were thus stratified by the Karnofsky performance score or interval from diagnosis to transplant, according on histology type. For TRM, nonproportional hazards were identified for type of graft (indolent histology patients) and use of G-CSF or GM-CSF (aggressive histology patients). Therefore, type of graft was entered into the Cox model for TRM for indolent NHL model as a time varying covariate, with early (<12 months) and late (≥12 months) effects for peripheral blood. Similarly, G-CSF or GM-CSF to promote engraftment was entered into the TRM for aggressive NHL model as a time varying covariate, with early (<8 months) and late (≥8 months) effects for recipients who received growth factors. The 8 Cox models were built using a forward stepwise selection process and covariates that attained a value of $P \leq .05$ were considered statistically significant and held in the final model (again with the exception that age group was forced into all models). For all outcomes of interest, interactions between age group and all covariates were tested before and after the model building. For relapse, there was a significant interaction between year of transplant and the effect of age for indolent NHL. In other words, age had a different effect depending on whether the patient was transplanted between 1990 and 1994, 1995 and 1996, 1997 and 1998, or 1999 and 2000. Therefore, the comparisons between age groups for this model are presented separately for each year of

Table 3A. Multivariate Analysis of Relapse for Follicular Grade I/II NHL

Variables	N	Relative Risk of Relapse (95% CI)	*P*-Value
Main effect of age*			
Year of transplant: 1990-1994			
Age ≥55 versus <55	375	1.35 (0.95-1.94)	.10
Year of transplant: 1995-1996			
Age ≥55 versus <55	170	0.76 (0.48-1.21)	.25
Year of transplant: 1997-1998			
Age ≥55 versus <55	143	1.12 (0.69-1.82)	.64
Year of transplant: 1999-2000			
Age ≥55 versus <55	75	2.66 (1.32-5.37)	.006
Other significant covariates			
Disease status at transplant†			
(1) CR1	97	1.00	<.001‡
(2) PIF-sensitive	141	1.66 (1.13-2.45)	.010
(3) PIF-resistant	22	3.23 (1.79-5.81)	<.001
(4) REL-sensitive	209	1.93 (1.35-2.77)	<.001
(5) REL-resistant	46	2.58 (1.62-4.11)	<.001
(6) CR2+	125	1.16 (0.77-1.75)	.47
(7) REL-untreated/unknown	29	1.44 (0.82-2.53)	.20
(8) PIF-untreated/unknown	10	1.80 (0.70-4.59)	.22
(9) Unknown	84	1.35 (0.86-2.11)	.19

CR indicates complete remission; PIF, primary induction failure; NHL, non-Hodgkin's lymphoma; CI, confidence interval.
Additional tests:
1. Overall 1 degree of freedom test for age (≥55 versus <55): $P = .006$.
2. Overall 3 degree of freedom test for year of transplant: $P = .002$.
3. Overall 3 degree of freedom test for Age × Year of transplant: $P = .027$.
*There is a significant interaction between the effects of age and year of transplant on the risk of relapse ($P = .03$) such that the effect age differs with the year of transplant.
†Other significant pairwise comparisons: $P_{23} = .016$; $P_{26} = .040$; $P_{36} \leq .001$; $P_{39} = .004$; $P_{46} = .001$; $P_{52} = .036$; $P_{56} \leq .001$; $P_{59} = .007$; $P_{73} = .020$; $P_{75} = .049$.
‡Eight degrees of freedom.

Table 3B. Multivariate Analysis of Relapse for Follicular Grade III/Diffuse Large B Cell/Immunoblastic NHL

Variables	N	Relative Risk of relapse (95% CI)	*P*-value
Main effect of age			
<55	1294	1.00	.002
≥55	615	1.22 (1.08-1.38)	
Other significant covariates			
Disease status at transplant*			
(1) CR1	221	1.00	<.001†
(2) PIF-sensitive	293	2.28 (1.76-2.95)	<.001
(3) PIF-resistant	98	4.07 (2.98-5.55)	<.001
(4) REL-sensitive	570	2.34 (1.85-2.97)	<.001
(5) REL-resistant	155	4.08 (3.07-5.43)	<.001
(6) CR2+	324	1.34 (1.03-1.74)	.031
(7) REL-untreated/unknown	75	2.44 (1.72-3.46)	<.001
(8) PIF-untreated/unknown	15	1.72 (0.75-3.93)	.20
(9) Unknown	158	2.62 (1.97-3.48)	<.001

CR indicates complete remission; PIF, primary induction failure; NHL, non-Hodgkin's lymphoma; CI, confidence interval.
*Other significant pairwise comparisons: $P_{23} \leq .001$; $P_{26} \leq .001$; $P_{36} \leq .001$; $P_{39} = .004$; $P_{43} \leq .001$; $P_{45} \leq .001$; $P_{46} \leq .001$; $P_{52} \leq .001$; $P_{56} \leq .001$; $P_{58} = .040$; $P_{59} = .001$; $P_{73} = .005$; $P_{75} = .003$; $P_{76} \leq .001$; $P_{83} = .04$; $P_{96} \leq .001$.
†Eight degrees of freedom.

transplantation (see Table 3A). Overall, covariate effects were tested using Wald test. All computations were made using the procedures PHREG and TPHREG in the statistical package SAS Version 9.1 for Unix. All multivariate models were examined for center effects using a random effects or frailty model [21]; there were no significant center effects.

RESULTS

Table 1 shows the patient-, disease-, and transplant-related characteristics of the 2754 patients included in the study according to age group (≥55 years versus <55 years) and histology type. The median age in the 2 age groups was 61 years (range: 55-73 years) and 45 years (range: 18-55 years) respectively, and younger patients were more likely to have follicular lymphoma (32% versus 21%). Combining patients from the 2 histology types, Karnofsky performance score at transplant did not differ significantly, but younger patients were more likely to have B symptoms at diagnosis (38% versus 31%), have primary refractory disease (24% versus 15%), receive bone marrow rather than peripheral blood as the graft source (30% versus 19%), and undergo a TBI-containing regimen (31% versus 22%).

Figures 1 and 2 show the univariate probabilities of all outcomes of interest after transplantation according to age group for indolent histology patients. At 1-, 3- and 5-years after transplant younger patients had a lower probability of relapse and a higher probability of DFS and OS. At 5 years after transplant, TRM did not differ significantly between age groups, but relapses were significantly higher, 8% versus 7% and 55% versus 63%, for subjects <55 years versus ≥55 years, respectively. DFS and OS rates at 5 years also favored younger patients, 37% versus 29% and 60% and 54%, respectively, Similarly, the younger aggressive histology patients had a lower probability of TRM and relapse and a higher probability of DFS and OS compared to subjects age >55 years (Figures 3 and 4). Specifically, at 5 years, TRM rates were significantly lower in younger patients (9% versus 15%) as were relapse rates (59% versus 66%), respectively. Correspondingly, DFS and OS rates were superior in the younger patient population, 32% versus 19% and 47% versus 30%, respectively.

Tables 2A and B show the multivariate analysis of TRM for older versus younger patients in both histologic subgroup types, respectively. After adjusting for other covariates, aggressive histology patients 55 years and older were 1.86 times more likely to have TRM than younger patients (95% confidence interval [CI] 1.43-2.43, $P < .001$). Age, however, was not a factor in the indolent histology group ($P = .54$). Other factors found to be associated with an increased TRM in the more aggressive histology patients were poor performance status, chemoresistant disease before transplant,

Table 4A. Multivariate Analysis of Overall Survival for Follicular Grade I/II NHL*

Variables	N	Relative Risk of Death (95% CI)	*P*-Value
Main effect of age			
<55	615	1.00	.024
≥55	173	1.33 (1.04-1.71)	
Other significant covariates			
Disease status at transplant†			
(1) CR1	101	1.00	<.001‡
(2) PIF-sensitive	145	1.39 (0.90-2.14)	.14
(3) PIF-resistant	22	2.89 (1.53-5.46)	.001
(4) REL-sensitive	218	1.82 (1.23-2.71)	.003
(5) REL-resistant	47	3.27 (1.99-5.39)	<.001
(6) CR2+	129	1.44 (0.92-2.23)	.11
(7) REL-untreated/unknown	32	1.48 (0.83-2.65)	.19
(8) PIF-untreated/unknown	10	3.31 (1.44-7.58)	.005
(9) Unknown	84	2.09 (1.32-3.33)	.002
Year of transplant§			
(1) 1999-2000	81	1.00	.005¶
(2) 1990-1994	383	2.08 (1.32-3.28)	.002
(3) 1995-1996	174	1.54 (0.95-2.51)	.080
(4) 1997-1998	150	1.74 (1.05-2.87)	.030

CR indicates complete remission; PIF, primary induction failure; NHL, non-Hodgkin lymphoma; CI, confidence interval.
*This Cox model was stratified on Karnofsky performance score at transplant (ie, ≥90% and <90%).
†Other significant pairwise comparisons: $P_{23} = .014$; $P_{29} = .045$; $P_{36} = .021$; $P_{45} = .004$; $P_{52} \leq .001$; $P_{56} \leq .001$; $P_{75} = .008$; $P_{82} = .03$; $P_{86} = .040$.
‡Eight degrees of freedom.
§Other pairwise comparisons: $P_{23} = .027$; $P_{24} = .24$; $P_{34} = .49$.
¶Three degrees of freedom.

Table 4B. Multivariate Analysis of Overall Survival for Follicular Grade III/Diffuse Large B Cell/Immunoblastic NHL*

Variables	N	Relative Risk of Death (95% CI)	*P*-Value
Main effect of age			
<55	1334	1.00	<.001
≥ 55	632	1.50 (1.33-1.69)	
Other significant covariates			
Karnofsky performance score at transplant†			
(1) ≥90%	1200	1.00	<.001‡
(2) <90%	712	1.35 (1.20-1.54)	<.001
(3) Missing	54	0.93 (0.67-1.32)	.038
Disease status at transplant§			
(1) CR1	228	1.00	<.001¶
(2) PIF-sensitive	305	1.60 (1.23-2.07)	<.001
(3) PIF-resistant	100	3.09 (2.27-4.21)	<.001
(4) REL-sensitive	586	1.92 (1.50-2.45)	<.001
(5) REL-resistant	159	3.94 (2.98-5.21)	<.001
(6) CR2+	330	1.54 (1.17-2.02)	.002
(7) REL-untreated/unknown	78	2.51 (1.79-3.52)	<.001
(8) PIF-untreated/unknown	16	1.85 (0.96-3.57)	.07
(9) Unknown	164	2.36 (1.78-3.15)	<.001
Conditioning regimen			
No TBI	1526	1.00	.009
TBI	440	1.20 (1.05-1.37)	
Year of transplant⊥			
(1) 1999-2000	295	1.00	.008**
(2) 1990-1994	696	1.36 (1.13-1.65)	.002
(3) 1995-1996	499	1.24 (1.02-1.52)	.032
(4) 1997-1998	476	1.14 (0.93-1.40)	.20

CR indicates complete remission; PIF, primary induction failure; NHL, non-Hodgkin lymphoma; TBI, total body irradiation, CI, confidence interval.
*This Cox model was stratified on interval from diagnosis to transplant (ie, ≥12 months and <12 months).
†Other pairwise comparisons: $P_{23} = .70$.
‡Two degrees of freedom.
§Other significant pairwise comparisons: $P_{23} \leq .001$; $P_{29} = .002$; $P_{36} \leq .001$; $P_{43} \leq .001$; $P_{45} \leq .001$; $P_{46} = .016$; $P_{52} \leq .001$; $P_{56} \leq .001$; $P_{58} = .022$; $P_{59} \leq .001$; $P_{72} = .004$; $P_{75} = .004$; $P_{76} = .001$; $P_{96} < .001$.
¶Eight degrees of freedom.
⊥Other pairwise comparisons: $P_{23} = .22$; $P_{24} = .025$; $P_{34} = .31$.
**Three degrees of freedom.

>12 months duration from diagnosis to transplant, and use of purging. For the indolent histology patients, significant covariates for increased TRM included use of bone marrow rather than blood as the graft source (however, this effect was no longer statistical significant in patients surviving >12 months posttransplant) and a TBI-containing conditioning regimen.

Tables 3A and B show the multivariate analysis of relapse. There was a statistically significant increase in risk of relapse for older patients (≥55 years) among patients with more aggressive NHL histologies (relative risk [RR] 1.22, 95% CI 1.08-1.38, $P = .002$). However, older patients with indolent histologies had an increased risk of relapse only if they were transplanted in the time period of 1999 to 2000. After adjusting for other covariates, both the indolent and the aggressive lymphoma histology patients with primary induction failure (PIF) and relapsed disease were at increased risk for lymphoma recurrence.

Similar results were noted for treatment failure (ie, inverse of DFS) for both histologic groups for the effect of age (a consistent effect confined to the aggressive subtype) and disease status at transplant. For the indolent histology group, age did not affect treatment failure (inverse of DFS), but disease status at transplant was the major determinate of outcome. The relative risk of treatment failure (95% CI) was significantly higher for patients who were primary induction failure sensitive (1.64 [1.15-2.32] times, $P = .006$), primary induction failure resistant (2.74 [1.59-4.73] times, $P < .001$], relapse sensitive (1.93 [1.39-2.68] times, $P < .001$), and relapse resistant (2.55 [1.66-3.93] times, $P < .001$). On the other hand, older age aggressive NHL patients were 1.32 (1.18-1.48) times more likely to fail than younger patients. Similar to the indolent NHL population, disease status at transplant again was a major determinant of outcome. The relative risk of treatment failure (95% CI) was significantly higher for patients who were primary induction failure sensitive (2.03 [1.61-2.56] times, $P < .001$), primary induction failure resistant (3.43 [2.57-4.58] times, $P < .001$), relapse sensitive (2.11 [1.71-2.61] times, $P < .001$) relapse resistant (3.89 [3.01-5.02] times, $P < .001$), and with second CR or beyond (1.47 [1.16-1.86] with times, $P = .001$). The use of TBI in the conditioning regimen and poor performance status were associated with a statistically significant increase in treatment failures in the aggressive lymphoma subgroup (1.16 [1.02-1.31], $P = .027$).

Table 5. Characteristics of NHL Patients More Than Age 65 Years Undergoing Autologous HCT from 1990 to 2000 and Reported to the CIBMTR

Variable	N (%)
Number of patients	149
Age, median (range), years	67 (65-73)
Male sex	71 (48)
Karnofsky performance score at transplant	
<90	61 (41)
≥90	87 (59)
Missing	*1*
Histology	
Follicular grade I/II	21 (14)
Follicular grade III/DLBCL/Immunoblastic NHL	128 (86)
Disease stage at diagnosis	
I or II	59 (40)
III or IV	87 (58)
Unknown	3 (2)
B symptoms at diagnosis	
Absent	91 (61)
Present	40 (27)
Unknown	18 (12)
Disease status at transplant	
CR1	10 (7)
CR2+	33 (24)
PIF-sensitive	18 (13)
PIF-resistant	2 (1)
REL-sensitive	48 (35)
REL-resistant	15 (11)
REL-untreated/unknown	13 (9)
Missing	*10*
Chemosensitivity at transplant	
Sensitivity	109 (73)
Resistant	24 (16)
Untreated/not evaluable/unknown	16 (11)
Interval from diagnosis to transplant	
<12 months	34 (23)
≥12 months	115 (77)
Graft type	
Bone marrow	17 (11)
Peripheral blood	132 (89)
Use of involved-field radiation	6 (4)
Use of TBI	19 (13)
Year of transplantation	
1990-1994	21 (14)
1995-1996	32 (22)
1997-1998	54 (36)
1999-2000	42 (28)
In vitro purging performed	10 (7)
G-CSF or GM-CSF to promote engraftment	134 (90)
New malignancy	
Solid tumor	3 (2)
Skin cancer	1 (1)
New malignancy, not specified	5 (3)
None	140 (94)
Median follow-up of survivors, months	69 (3-139)

CR inidicates complete remission; PIF, primary induction failure; TBI , total-body irradiation; GF, growth factors; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; NHL, non-Hodgkin lymphoma; CIBMTR, Center for International Blood and Marrow Transplant Research.

Tables 4A and B show the multivariate analysis of OS for the main effect of age. The relative risk of death was higher in older patients (≥55 years) in indolent histology as well as in aggressive NHL patients. After adjusting for other covariates, risk of mortality was statistically significantly increased in patients whose disease was not controlled (relapse or primary induction failure). Again, the use of TBI in the conditioning regimen and poor performance status were associated with a statistically significant increase in mortality in the aggressive lymphoma subgroup.

We further explored outcome in the oldest patient population, that is, N = 149 subjects aged over 65 years (Table 5). Compared to those patients <65 years (N = 2605), older individuals were statistically more likely to have a lower performance status ($P = .044$), have aggressive rather than indolent histologies ($P < .001$), have more advanced disease stage ($P = .032$), yet more sensitive disease ($P = .002$), and undergo HCT beyond 12 months after diagnosis ($P = .002$). Table 6 shows the univariates for the 4 outcomes of interest for the older patient group. At 5 years after HCT, probabilities of TRM and relapse were 14% (95% CI 9-20) and 66% (95% CI 58-73), respectively. These data translate into 5-year DFS and OS probabilities of

Table 6. Univariate Probabilities of Outcomes for NHL Patients More Than Age 65 Years Undergoing Autologous HCT from 1990 to 2000

Outcome Event	N	Prob (95% CI)*
Treatment-related mortality	147	
@ 1 year		11 (7-17)
@ 3 years		13 (8-19)
@ 5 years		14 (9-20)
Relapse	147	
@ 1 year		60 (51-67)
@ 3 years		66 (58-73)
@ 5 years		66 (58-73)
Disease-free survival	147	
@ 1 year		29 (22-36)
@ 3 years		21 (15-28)
@ 5 years		20 (14-27)
Overall survival	149	
@ 1 year		50 (42-58)
@ 3 years		35 (28-43)
@ 5 years		29 (22-37)

PROB indicates probability; CI, confidence interval.
*Probabilities of treatment-related mortality and relapse were calculated using the cumulative incidence estimate. Disease-free survival and overall survival were calculated using the Kaplan-Meier product limit estimate.

Table 7. Causes of Death for NHL Patients Undergoing Autologous HCT from 1990 to 2000 Comparing <55 versus >55 Years of Age

	≤55 Years	>55 Years
Causes of death	N (%)	N (%)
Number of patients	1032	544
Primary disease	729 (71)	370 (68)
New malignancy	23 (2)	18 (3)
Graft-versus-host disease	5 (<1)	0
Interstitial pneumonia	48 (5)	32 (6)
Infection	48 (5)	30 (6)
Organ failure	55 (5)	41 (8)
Other cause	124 (12)	53 (9)

NHL indicates non-Hodgkin lymphoma; HCT, hematopoietic cell transplantation.

20% (95% CI 14-27) and 29% (95% CI 22-37), respectively. Table 7 shows causes of death for all patients using age 55 years as the breakpoint. The major cause of death in both age groups was recurrent lymphoma.

DISCUSSION

We report the outcomes and prognostic factors for 2754 patients with NHL who received autologous stem cell transplant between 1990 and 2000 and were reported to the CIBMTR, based on age groups older or <55 years. In multivariate analysis, older patients with more aggressive NHL histologies were 1.86 times more likely than younger patients to experience TRM. Outcomes reported in this study appear better than the considerably smaller series of patients with aggressive NHL histologies reported in the literature [22-29], some of which included aggressive [21-23,27] versus mixed indolent and aggressive [25-27,29] histologies. It should be noted that in many of these reports, including those by Bitran and colleagues [28] and Moreau and coworkers [24], the transplant was performed only if the patient had relapsed disease that was sensitive to salvage therapy. With the exception of Sweetenham et al. [22], all these authors used 60 years as their age cutoff. Although 55 years is a more optimal choice for our data, the analyses of Tables 2A/B-4A/B were repeated with 60 years as the age threshold. Although the point estimates for the effect of age varied slightly, the overall effect of age remained the same, as did the other significant covariates (data not shown). Further, in our series, TRM at up to 5 years did not exceed 8% for either age group for follicular grade I/II NHL patients.

Our observational database collects information prospectively and such data likely are a more representative reflection of the practice of HCT in the community. It is difficult to make effective comparisons between our results and those reported in the literature for these patients. Published results from single center studies are often unadjusted (univariate outcomes), and study entry criteria, treatment, and attribution of cause of death are likely to vary across centers and studies. As well, the observational data collected by CIBMTR may include patients previously reported in single center experiences. Our reported 6% TRM at 1 year and 7% at 3 years for the indolent histology group for both older and younger patients compares favorably with the experiences reported in the 2 largest series [22,27], although these communications included mostly aggressive histologies. In the aggressive NHL patients, TRM rates at 3 years and 5 years after transplant of 14% (95% CI 11-17) and 15% (95% CI 12-18), respectively, in the over 55-year age group compare favorably with the 22.4% reported by Gopal et al [27]. Those investigators reported both infectious and noninfectious events as causes of death, the former postulated to be because of a protracted time to immune reconstitution in the older patients. Further, for patients >55 years, the lower TRM in the indolent population compared to the aggressive histology group may reflect an inherent selection bias, that is, other therapeutic options may be available for elderly indolent NHL patients. As anticipated, poor performance status at transplant and a longer time from diagnosis to transplant was associated with a toxic death. The adverse effect of hematopoietic growth factor use in this patient population has been previously described [30]. Data from the European Group for Blood and Marrow Transplantation (EBMT) and reported by Sweetenham et al [22] described a 38% TRM for patients aged >55 years. A comparison within the EBMT database for the patients aged <55 years showed a significantly lower TRM, 12% versus 38% ($P = .03$). On the other hand, in our series those subjects aged <55 years had a reduced TRM of 9% at 3 years (95% CI 7-10) as well as at 5 years (95% CI 7-11). Use of bone marrow rather than blood as the stem cell source and use of a TBI-containing regimen portended for TRM in patients with the aggressive lymphoma histology. The EBMT also reported that TBI-based preparative regimens contributed to a higher toxic death rate [22].

We also demonstrated that risk of relapse was greater for all older patients in the more aggressive histologic group, but only for older patients transplanted between 1999 and 2000 in the indolent histologic group. As anticipated, advanced or persistent disease in both indolent and aggressive histologic patient populations was associated with an increased risk of relapse compared to remission. Similarly, chemotherapy resistance prior to transplant was associated with an increased risk of relapse.

These data show that older patient age was associated with a statistically significant increased risk of treatment failure only in the aggressive histology subset (1.32-fold increase, $P < .001$) compared to the indolent histology group; however, in both groups age ≥55 years was associated with increased mortality (RR 1.50, $P < .001$ and RR 1.33, $P = .024$, respectively). Other factors associated with treatment failure and increased death in both patient populations included persistent, relapsed, or chemoresistant disease. Gopal and colleagues [27] reported superior survival in patients with responsive, relapsed disease as OS at 4 years was 39% in sensitive disease versus only 15% in resistant NHL. In the aggressive histologic group, poor performance status as well as use of TBI in the preparative regimen significantly increased the risk of treatment failure and reduced OS. Our data did not indicate that blood rather than bone marrow as the graft source was associated with an improved OS, in contrast to the European experience generated in advanced Hodgkin and high-grade NHL patients [31].

Limitations of these analyses include inability to account for patients who may not have been considered for HCT, that is, careful selection and exclusion of older patients deemed unfit for HCT. Also, perhaps other inherent selections biases are in operation such as offering HCT only for follicular NHL patients with highly aggressive disease who are young versus designating the older patients for other therapies, for example, age and disease biologic behavior discrimination. Another limitation of this report is the observation that various histologic classifications were in use during this long period of patient accrual and follow-up. All studies are subject to changing lymphoma classification over time, but the histologies noted were those reported by each institution and the diagnoses are consistent within the era of HCT. Pathology materials are not routinely subject to secondary review.

After adjusting for other important characteristics, older patients transplanted between 1990 and 2000 have a greater risk of adverse outcomes than those <55 years. Although changes in transplantation have allowed more advanced age patients to be considered for HCT, these patients have worse outcomes compared to their younger counterparts. Despite this observation, some older patients still should be considered for potential cure using HCT. Buadi and colleagues [32] at the Mayo Clinic reported a series of 93 intermediate-grade NHL patients at least 60 years of age (including 24 over age 70 years) who underwent HCT. TRM was 5.4% and 4-year event-free survival (EFS) was 38%, results that did not differ from a cohort less than age 60 years (2.2% and 42%, $P = .10$, respectively). Although a small series from a single institution, this group showed that good results can be obtained in older patients using careful patient selection and a non-TBI regimen. Another recent single institution trial reported by Wildes and colleagues [33] showed similar toxicities and survival for patients older than 60 years compared to younger patients. These investigators observed that after controlling for age, comorbidities significantly influenced OS.

The 149 patients age >65 years described herein were more likely to have a worse performance status, more advanced disease, and a more aggressive histology compared to their younger counterparts in our data set. Such information may help account for the 14% (95% CI 11-19) 5-year TRM. This patient group also had lower 5-year DFSs and OSs, 20% (95% CI 14-27) and 29% (95% CI 22-37), respectively. Seventy percent of elderly patients died because of lymphoma, a rate essentially the same as in the younger patients (69%). A series of 99 consecutive relapsed NHL patients age older than 65 years reported recently by Hosing and coworkers [34] showed an 8% cumulative nonrelapse mortality at 26 months and a 61% 3-year OS. They found that even elderly patients with a comorbidity index >2 had acceptable outcomes but were at higher risk for developing significant toxicity.

Additional strategies to reduce these risks for TRM and relapse should be explored. Possible strategies could include individual patient dosing as employed with busulfan-containing regimens in the allograft setting [35], and use of targeted radioimmunoconjugates, which may facilitate effective delivery of radiation to tumor cells without causing excessive toxic effect to normal tissues [36,37]. Ultimately, these and other approaches in older patients require further study.

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