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Conditional Long-Term Survival after Autologous Hematopoietic Cell Transplantation for Diffuse Large B Cell Lymphoma

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A B S T R A C T

Autologous hematopoietic cell transplantation (AHCT) is standard therapy for patients with chemosensitive, relapsed, diffuse large B cell lymphoma (DLBCL). We performed a retrospective cohort study to delineate subsequent (conditional) and relative survival in 371 adult patients with DLBCL who underwent AHCT between 2000 and 2014 and had survived for 1, 2, 3, or 5 years after transplant. The probability of overall survival at 10 years after AHCT was 62%, 71%, 77%, and 86%, respectively, for the 4 cohorts, whereas that of progression-free survival (PFS) was 55%, 65%, 72%, and 81%, respectively. The respective cumulative incidence of nonrelapse mortality (NRM) at 10 years after transplantation was 13%, 12%, 11%, and 8%, respectively. In multivariable analysis, older age was associated with greater mortality risk among all but 5-year survivors; relapse within the landmark time was associated with greater mortality risk in all groups. Older age and relapse within the landmark time were associated with worse PFS in all groups. Standardized mortality ratio (SMR) was significantly higher than an age-, gender-, and race-matched general population, with the magnitude of SMR decreasing as the landmark time increased (4.0 for 1-year, 3.0 for 2-year, 2.4 for 3-year, and 1.8 for 5-year survivors). Our study provides information on long-term survival and prognosis that will assist in counseling patients with DLBCL who have received AHCT. Survival improves with longer time in remission post-transplant, although patients continue to remain at risk for NRM, underscoring the need for continued vigilance and prevention of late complications.

INTRODUCTION

Autologous hematopoietic stem cell transplantation (AHCT) is standard therapy for chemosensitive, relapsed, diffuse large B cell lymphoma (DLBCL) and provides the potential for cure or prolonged remission [1,2]. Relapse is the primary cause of treatment failure after AHCT and typically occurs early post-transplant [3]. Many patients stay in remission, and survival after AHCT for DLBCL has been well described in large patient cohorts, although there is still a gap in life expectancy as compared with the general population [4]. However, a common question in clinical practice is the likelihood of subsequent survival for a given patient conditional to staying in remission for a certain time period post-transplant. This conditional survival is based on the principle that the mortality risk for a cohort of patients who are alive at a given time point changes in a measurable way as time evolves from the date of transplant [5,6]. Therefore, we performed a retrospective cohort study to delineate conditional survival and prognostic factors for late mortality in patients with DLBCL who had survived 1, 2, 3, and 5 years after AHCT. We also describe survival for these cohorts relative to their general population control subjects.

METHODS

Using our institutional Blood and Marrow Transplant Program database, we identified 371 consecutive adult patients (≥18 years) with DLBCL who received AHCT from 2000 to 2014. Our database prospectively collects clinical and outcome information on transplant recipients at our program. The study was conducted under review of Cleveland Clinic's Institutional Review Board. Written informed consent was obtained from all participants.

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The primary objective of our analysis was to describe and identify prognostic factors for overall survival (OS) and progression-free survival (PFS) among patients who had survived for at least 1 year (n = 272), 2 years (n = 232), 3 years (n = 203), or 5 years (n = 157) after AHCT. All patients who were alive were included, irrespective of whether their lymphoma had relapsed. The event for OS was all-cause mortality. The events corresponding to PFS were progression, relapse, or all-cause mortality. Secondary endpoints were relapse mortality (RM) and nonrelapse mortality (NRM). All outcomes were determined from time of AHCT.

Patient demographics were summarized using descriptive statistics. Outcomes were estimated with the Kaplan-Meier method (OS, PFS) or by cumulative incidence (RM, NRM). Multivariable analyses using stepwise Cox regression were performed to evaluate prognostic factors for OS and PFS; variable entry criterion of $P \leq .10$ and a variable retention criterion of $P \leq .05$ were used to identify multivariable prognostic factors.

Variables considered included year of AHCT, age at AHCT, sex, race, international prognostic index score at diagnosis and at AHCT, B symptoms at diagnosis and at AHCT, history of transformation, stage, disease risk, time from diagnosis to transplant, performance status at transplant, number of prior chemotherapy regimens, prior radiation therapy, prior use of rituximab, days of apheresis, $CD34^+$ and TNC doses, days to neutrophil and platelet engraftment, duration of transplant hospitalization, and relapse before inclusion in the cohort (eg, relapse within 2 years of AHCT for the 2 year survivor cohort). Results are presented as hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs).

For relative survival we estimated the standardized mortality ratio (SMR) and its 95% CI within each survivor cohort as described by Finkelstein et al. [7]. SMR is the ratio of the number of observed deaths among study patients to the expected number of deaths in an age-, gender-, and race-matched healthy population.

All P values are 2-sided, and $P < .05$ was considered to be significant. Unless otherwise noted, analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Patient Characteristics

Table 1 summarizes patient demographics for 1-, 2-, 3-, and 5-year survivors. Across all cohorts, around 60 of the patients were men, more than 70 were stage III/IV, more than 70 had low/low-intermediate international prognostic index at diagnosis and at transplant, and less than 5 had poor performance status (defined as Eastern Cooperative Oncology Group > 1 or Karnofsky performance status < 80). All patients received peripheral blood stem cell grafts and had chemosensitive disease. Among the 4 cohorts of survivors, 77% to 82% underwent chemotherapy mobilization, 26% to 28% had received prior radiation, 79% to 82% had received prior rituximab, and 97% received the busulfan/cyclophosphamide/etoposide conditioning regimen.

Outcomes

Table 2 shows 6-, 8-, and 10-year estimates of OS, PFS, RM, and NRM after AHCT for all 4 cohorts. OS and PFS improved with increasing survival after transplantation, whereas RM and NRM decreased over time. Relapse was the primary cause of mortality in 1-year survivors (65% of deaths) and 2-year survivors (57% of deaths). Among 3-year survivors, however, patients died equally of relapse and non-relapse causes (50% due to relapse), whereas more patients died of non-relapse causes among 5-year survivors (39% of deaths due to relapse). Secondary malignancy was the most common cause of nonrelapse death in all 4 time cohorts; it accounted for 16% of all deaths among 1-year survivors, 25% in 2-year survivors, 29% in 3-year survivors, and 26% in 5-year survivors.

Supplementary Tables 1 to 4 provide detailed results of univariate and multivariable analyses. Briefly, among other patient and disease characteristics evaluated in risk factor analysis, age at transplant and duration of hospitalization post-AHCT were major factors that had a statistically significant impact on OS and PFS. Older age (in 10-year increments) was associated with greater mortality risk among 1-year survivors (HR, 1.37; 95% CI, 1.13 to 1.65), 2-year survivors (HR, 1.49; 95% CI, 1.16 to 1.91), and 3-year survivors (HR, 1.47; 95% CI, 1.11 to 1.95) but not among 5-year survivors. Supplementary Table 5 and Supplementary Figure 1 provide conditional survival by age for 1-, 2-, 3-, and 5-year survivors. Older age at transplant was associated with worse PFS among all 4 cohorts (HR, 1.45, 1.48, 1.59, and 1.61, respectively). Prolonged hospital stay was used as a surrogate for early post-transplant complications. Hospital stay > 24 days was associated with lower OS for all 4 cohorts and lower PFS for 2-, 3-, and 5- year survivors (results not shown).

Standardized Mortality Ratio

In each cohort, survival was lower when compared with a general age-, gender-, and race-matched healthy population. As shown in Figure 1, these numbers improved and approached that of healthy peers with increasing post-transplant survival. SMR was 4.0 (95% CI, 3.2 to 5.1) for 1-year survivors, 3.0 (95% CI, 2.2 to 4.0), for 2-year survivors, 2.4 (95% CI, 1.7 to 3.4) for 3-year survivors, and 1.8 (95% CI, 1.1 to 2.9) for 5-year survivors. Noticeably, the magnitude of SMR decreased as the landmark time increased.

DISCUSSION

AHCT has become standard of care for a large number of otherwise life-threatening hematologic malignancies. Survivorship begins from day 0 of stem cell infusion and is associated with variable complications [8]. Although other studies have not looked at conditional survival among lymphoma patients receiving AHCT, relative mortality among transplant survivors has been described [9-11]. Overall, findings have been mixed, with some studies showing survival approaching that of the general population and others demonstrating continued elevation in SMR in this patient population. For instance, in a study by Bhatia et al. [10] of 854 patients with a variety of hematologic malignancies who had survived 2 years or more post-AHCT, mortality risk approached that of the healthy general population 10 years after transplant. On the other hand, in a retrospective study by Hill et al. [12] that included 309 patients with DLBCL who underwent AHCT, they concluded that although patients who do not relapse 5 years after AHCT are considered cured, their SMR does not return to baseline even 15 years after AHCT. In a Center for International Blood and Marrow Transplant Research study of 1367 lymphoma AHCT 2-year survivors, the SMRs remained elevated compared with the general population at 10 years post-transplant [11]. A study in New Zealand and Australia found that mortality among 1461 allogeneic or autologous transplant recipients with different hematologic malignancies begins to approach that of the general healthy population 6 years after transplant but remains consistently higher even up to 10 years out [13]. Pond et al. [14] described that the mortality risk in 1386 Canadian patients 6 years after allogeneic transplantation was most likely not transplant-related and proposed the definition of a long-term survivor as a patient who has survived 6 years after transplant. However, there is no predetermined cutoff for when mortality in transplant recipients matches that of the healthy general population, because of the differences in morbidity profiles each year survived post-transplant.

Our study provides personalized survivorship information for patients with DLBCL who receive AHCT and identifies risk factors for poor conditional survival after transplant. We show that the probability of surviving post-AHCT increases with longer follow-up post-transplant. After surviving 1 year

Table 1
Patient Characteristics

Characteristic	1-Year Survivors (n = 272)	2-Year Survivors (n = 232)	3-Year Survivors (n = 203)	5-Year Survivors (n = 157)
Median age at AHCT, yr (range)	56 (19-78)	56 (19-78)	55 (19-76)	53 (19-75)
Sex				
Male	165 (60.7)	140 (60.3)	120 (59.1)	96 (61.1)
Female	107 (39.3)	92 (39.7)	83 (40.9)	61 (38.9)
Race				
Non-Hispanic white	253 (93.0)	214 (92.2)	186 (91.6)	142 (90.4)
African American	14 (5.1)	14 (6.0)	13 (6.4)	11 (7.0)
Hispanic	4 (1.5)	3 (1.3)	3 (1.5)	3 (1.9)
Other	1 (.4)	1 (.4)	1 (.5)	1 (.6)
IPI at diagnosis				
Low/low intermediate	191 (74.3)	165 (74.7)	146 (74.5)	115 (73.7)
High intermediate/high	66 (25.7)	56 (25.3)	50 (25.5)	41 (26.3)
Unknown	15	11	7	1
IPI at AHCT				
Low/low intermediate	197 (73.2)	164 (71.6)	146 (72.3)	113 (72.4)
High intermediate/high	72 (26.8)	65 (28.4)	56 (27.7)	43 (27.6)
Unknown	3	3	1	1
B symptoms at diagnosis	121 (45.1)	106 (46.1)	96 (47.5)	78 (49.7)
B symptoms pre-AHCT	20 (7.4)	19 (8.2)	19 (9.4)	15 (9.6)
Transformed DLBCL	59 (21.7)	52 (22.4)	46 (22.7)	38 (24.2)
Stage at diagnosis				
I	21 (7.8)	15 (6.6)	12 (5.9)	9 (5.8)
II	37 (13.8)	31 (13.5)	28 (13.9)	22 (14.1)
III	62 (23.0)	52 (22.7)	44 (21.8)	34 (21.8)
IV	149 (55.4)	131 (57.2)	118 (58.4)	91 (58.3)
Unknown	3	3	1	1
Median time from diagnosis to AHCT, mo (range)	18.5 (.9-372.3)	18.4 (.9-372.3)	18.5 (.9-372.3)	16.1 (.9-372.3)
≥3 chemotherapy regimens before AHCT	73 (26.9)	59 (25.4)	50 (24.6)	35 (22.3)
Prior rituximab	221 (81.2)	192 (82.8)	167 (82.3)	124 (79.0)
Prior radiation	77 (28.3)	61 (26.3)	57 (28.1)	42 (26.8)
Performance status at AHCT				
Good (ECOG ≤ 1/Karnofsky performance status ≥ 80)	249 (95.8)	210 (95.5)	185 (96.4)	144 (98.0)
Poor (ECOG > 1/Karnofsky performance status <80)	11 (4.2)	10 (4.5)	7 (3.6)	3 (2.0)
Unknown	12	12	11	10
Disease risk category*				
Low	9 (3.3)	9 (3.9)	8 (3.9)	7 (4.5)
Intermediate	238 (87.5)	203 (87.5)	179 (88.2)	139 (88.5)
High	25 (9.2)	20 (8.6)	16 (7.9)	11 (7.0)
Chemotherapy mobilization	210 (77.2)	181 (78.0)	161 (79.3)	129 (82.2)
Mean $CD34^+$ dose, $\times 10^6$/kg (standard deviation)	8.99 (8.44)	9.04 (8.52)	9.49 (8.92)	10.36 (9.56)
Conditioning regimen				
Bu/Cy/VP	264 (97.1)	226 (97.4)	197 (97.0)	152 (96.8)
Other	8 (2.9)	6 (2.6)	6 (3.0)	5 (3.2)
Mean duration of AHCT hospitalization, days (standard deviation)	22 (3)	22 (2)	22 (2)	21 (92)
Relapse after AHCT but before inclusion in the cohort	41 (15.1)	36 (15.5)	34 (16.7)	23 (14.6)
Median follow-up of alive patients, mo (range)	95.9 (15.8-198.4)	96.9 (26.6-198.4)	108.2 (37.2-198.4)	119.0 (60.0-198.4)

Values are n (%) unless otherwise defined. IPI indicates international prognostic index; ECOG, Eastern Cooperative Oncology Group; Bu/Cy/VP, busulfan/cyclophosphamide/etoposide.

* Disease risk category includes low risk, first complete remission; intermediate risk, second or greater complete remission or partial remission; high risk, primary refractory or resistant relapse or never treated.

post-transplant, the likelihood of surviving to 10 years is approximately 62%, and after surviving the first 5 years the likelihood of surviving to 10 years increases to 86%. Relative mortality is shown to decrease with more time elapsed from transplant, providing evidence that the survival of AHCT recipients approaches that of their healthy peers. In our analysis that has looked at conditional survival in a cohort of longer-term survivors, the relative mortality approaches that of the general population. Our data provide helpful prognostic information to counsel patients who are further out from AHCT.

An important finding to note in our study is the change in pattern of mortality as patients survive longer post-AHCT. More patients died of relapse earlier post-transplant; however,

Table 2
Six-, 8-, and 10-Year Outcomes in AHCT Recipients with DLBCL Conditional to Surviving 1, 2, 3, and 5 Years after Transplant

Outcomes	1-Year Survivors	2-Year Survivors	3-Year Survivors	5-Year Survivors
OS				
At 6 yr after AHCT	71 (65-76)	81 (75-86)	88 (82-92)	98 (94-99)
At 8 yr after AHCT	66 (59-72)	75 (68-81)	81 (74-87)	90 (84-94)
At 10 yr after AHCT	62 (55-68)	71 (64-77)	77 (69-83)	86 (78-91)
PFS				
At 6 yr after AHCT	63 (57-69)	75 (69-80)	83 (77-88)	94 (89-97)
At 8 yr after AHCT	58 (51-64)	69 (62-75)	76 (68-82)	85 (77-90)
At 10 yr after AHCT	55 (48-61)	65 (58-72)	72 (64-87)	81 (73-87)
RM				
At 6 yr after AHCT	21 (16-26)	13 (9-18)	8 (4-12)	1 (.3-4)
At 8 yr after AHCT	23 (18-29)	15 (11-21)	11 (6-16)	5 (2-10)
At 10 yr after AHCT	25 (19-30)	17 (12-23)	12 (8-18)	7 (3-12)
NRM				
At 6 yr after AHCT	8 (5-12)	6 (3-10)	4 (2-8)	.7 (.01-3)
At 8 yr after AHCT	11 (7-16)	10 (6-14)	8 (4-13)	5 (2-10)
At 10 yr after AHCT	13 (9-18)	12 (8-17)	11 (6-16)	8 (4-13)

Values are estimate % (95% confidence intervals).

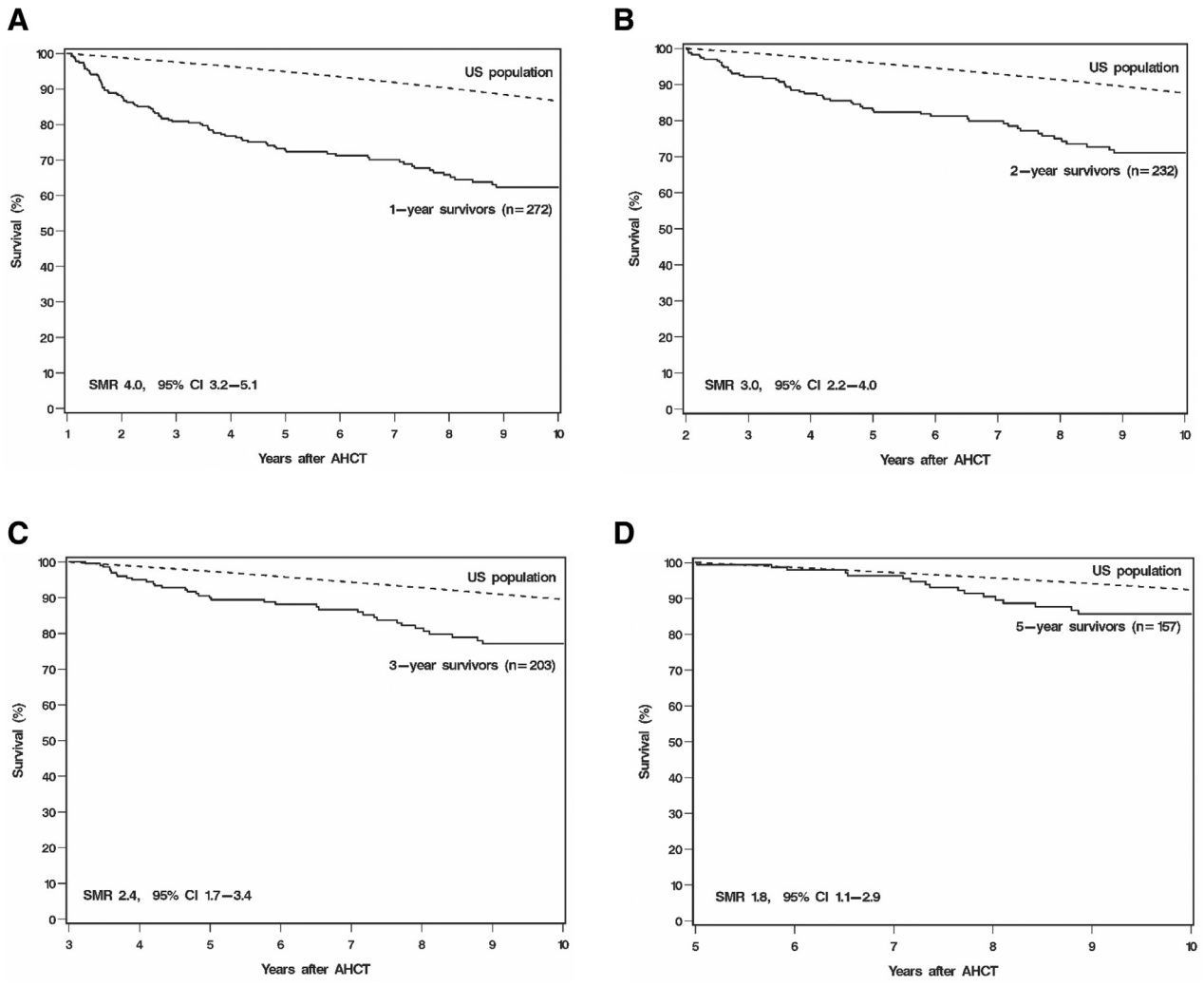

Figure 1. Relative mortality among survivors post-AHCT in patients with DLBCL compared with an age-, gender-, and race-matched US healthy population. (A) SMR for 1-year survivors was 4.0 (95% CI, 3.2 to 5.1). (B) SMR for 2-year survivors was 3.0 (95% CI, 2.2 to 4.0). (C) SMR for 3-year survivors was 2.4 (95% CI, 1.7 to 3.4). (D) SMR for 5-year survivors was 1.8 (95% CI, 1.1 to 2.9).

non-relapse causes became the predominant driver of mortality in patients who had survived for 5 years. Hill et al. [12] found that relapse is the major cause of mortality within the first 2 years after AHCT, whereas NRM is the major contributor of death 8 years after AHCT, with most common etiologies being respiratory failure and infection followed by secondary malignancies. In 2009 Majhail et al. [11] provided evidence among a cohort of 407 Hodgkin lymphoma patients and 960 non-Hodgkin lymphoma patients that the incidence of NRM exceeded 10% at the 10-year mark post-AHCT, mostly related to secondary malignancies and organ failure. Taken together, our study highlights the importance of continued long-term follow-up and screening for late complications of transplant [15-17].

In conclusion, the conditional survival of patients undergoing AHCT improves with time and approaches that of the general population on long-term followup. Our study also underscores the need for continued research on decreasing relapse risk and for surveillance, prevention and management of late complications in this population, ultimately providing evidence-based guidelines for long-term follow-up.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.09.012.

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