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Long-Term Outcomes Among Two-Year Survivors of Autologous Hematopoietic Cell Transplant for Hodgkin and Diffuse Large B-Cell Lymphoma

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Abstract

BACKGROUND—Autologous hematopoietic cell transplant (autoHCT) is a standard therapy for relapsed Hodgkin lymphoma (cHL) and diffuse large B-cell lymphoma (DLBCL); however, long-term outcomes are not well described.

METHODS—We analyzed survival, non-relapse mortality, late effects and subsequent malignant neoplasms (SMN) in 1617 patients who survived progression-free for ≥2 years after autoHCT for

cHL or DLBCL, between 1990 and 2008. The median age at autoHCT was 40 years; median follow-up was 10.6 years.

RESULTS—Five-year overall survival was 90% (95%CI, 87–92) for cHL and 89% (95%CI, 87–91) for DLBCL. The risk of late mortality compared with the general population was 9.6-fold higher for cHL patients (standardized mortality ratio [SMR] = 9.6) and 3.4-fold (SMR = 3.4) higher for DLBCL patients. Relapse accounted for 44% of late deaths. At least one late effect was reported in 9% of patients. A total of 105 SMN were confirmed, 44 in the cHL and 61 in the DLBCL group. By multivariate analysis, older age, male sex, Karnofsky score <90, total body irradiation (TBI) exposure, and higher numbers of lines of chemotherapy prior to autoHCT were risk factors for overall mortality in cHL. Risk factors in DLBCL were older age and TBI-exposure. A sub-analysis of 798 adolescent and young adult patients mirrored outcomes of the overall study population.

CONCLUSION—Despite generally favorable outcomes, two-year survivors of autoHCT for cHL or DLBCL have an excess late mortality risk when compared to the general population and experience an assortment of late complications.

Keywords

late effects; survival; non-relapse mortality; autologous hematopoietic cell transplant; Hodgkin lymphoma; diffuse large B-cell lymphoma

Introduction

High-dose chemotherapy followed by autologous hematopoietic cell transplant (autoHCT) remains the standard treatment for medically-fit patients with relapsed or refractory aggressive lymphomas.[1,2] Reported survival rates 3–5 years after autoHCT for classical Hodgkin lymphoma (cHL) and diffuse large B-cell lymphoma (DLBCL) range between 40 and 70%.[2–8] Treatment failure is most commonly due to relapse or progression of the underlying disease, which primarily occurs within the first two years after autoHCT.[1] For those patients who survive the initial post-autoHCT period, long-term outcomes are not well described.

Prior reports of long-term outcomes after autoHCT were limited by short follow-up times, inclusion of patients who received older therapies, or small, non-representative patient cohorts. The first major study of late mortality described outcomes of 854 patients who survived at least two years after autoHCT for leukemia or lymphoma, between 1981–1998.[9] With a median follow-up of 7.6 years and 68% having received total-body irradiation (TBI) based preparative regimens, the cohort had a 13-fold increased risk of late death compared with the general population. Subsequent reports have confirmed an increased risk of late mortality.[10–13] Additional, mostly single center studies have reported high rates of organ impairments, functional limitations, and subsequent malignant neoplasms (SMN) in autoHCT survivors.[13–15]

To address the gaps in the literature, we selected a representative, multicenter cohort of two-year disease-free survivors of autoHCT for cHL or DLBCL who were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). We sought to evaluate:

(1) long-term survival and mortality risk as compared to the general population, (2) SMN, (3) non-malignant late effects and (4) predictive factors for worse long-term outcomes. Since cHL is the most common cancer in adolescents and young adults (AYA), we also conducted a sub-analysis of AYA survivors.[16]

Methods

Data Source

The CIBMTR is a voluntary working group comprised of over 450 transplantation centers worldwide that contribute detailed hematopoietic cell transplant data to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program in Minneapolis. Participating centers are required to report all transplants consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally. Computerized checks for discrepancies, physician's review of submitted data and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants and are under the guidance of the institutional review board of the National Marrow Donor Program.

The CIBMTR collects transplant-essential data for all patients, which includes demographic, disease type and stage, pre-transplant chemotherapy, graft type, preparative regimen, development of a new malignancy, survival, relapse and cause of death data. A subset of patients, selected by a weighted randomization scheme, also have comprehensive research level data collected. Late effects data are obtained from this subset and therefore, only this group of patients was included in the current study. The presence of the following specific late effects are reported: avascular necrosis, bronchiolitis obliterans, pulmonary hemorrhage, cataracts, congestive heart failure, myocardial infarction, diabetes/hyperglycemia, gonadal dysfunction/infertility requiring hormone replacement, growth hormone deficiency/growth disturbance, hypothyroidism, hemorrhagic cystitis/hematuria requiring medical intervention, non-infectious liver toxicity, pancreatitis, post-transplant microangiopathy-thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, renal failure or stroke/seizure. The data are collected pre-transplant, 100 days and six months post-transplant and then annually.

To confirm diagnoses of SMN, pathology reports were obtained from reporting transplant centers. Any new malignancy diagnosis that could not be confirmed on central review was not included in the analysis.

Study population

The study population consisted of AYA and older adults (age > 39 years) who had survived progression-free for ≥2 years following autoHCT for cHL or DLBCL between January 1, 1990 and December 31, 2008. Patients ages 15–39 years were characterized as AYA, based on the National Cancer Institute's definition.[17] The study was restricted to patients treated in the United States and Canada.

Of 5171 patients undergoing their first autoHCT for cHL or DLBCL at age ≥15 years, 1023 were excluded based on their transplant center's location or completeness of follow-up.

Another 2250 patients were excluded because of death (n=1594), relapse (n=584), or loss to follow-up (n=72) within two years of autoHCT. Other exclusion criteria were nodular lymphocyte predominant HL (n=5), low-grade lymphomas or chronic lymphocytic leukemia transforming to DLBCL (n=102), known HIV positive status (n=53), subsequent transplant within two years of the first transplant (n=52), a pre-autoHCT history of another malignancy (other than non-melanomatous skin cancers, n=56), and missing CIBMTR forms (n=13). The final study cohort consisted of 1617 patients from 134 centers.

Outcomes

Outcomes studied included overall survival (OS), progression-free survival (PFS), relapse and non-relapse mortality (NRM). OS was defined as time to death from any cause and was censored at last point of contact. For PFS, a patient was considered a treatment failure at the time of progression/relapse or death from any cause. Relapse was defined as progressive disease after autoHCT or disease recurrence after a complete remission; death in remission was considered a competing risk. NRM was defined as death without evidence of progression/relapse; relapse was considered a competing risk.

Additional outcomes included the development of SMN and non-malignant organ impairments ≥2 years after autoHCT. Late effects were censored at the time of second transplant or relapse. Only the specific organ impairments collected on the CIBMTR forms described above were analyzed.

Statistical analysis

Descriptive statistics were calculated for patient demographic, disease and treatment-related variables. The Kaplan-Meier method was used to estimate the probability of overall survival, which was calculated from the two-year landmark after autoHCT to the date of death or last follow-up. The cumulative incidence function was used to estimate relapse, relapse-related death, and NRM. The frequencies of individual late effects (censored at relapse or second transplant) were calculated. In addition, the cumulative incidence of developing a SMN, ≥1 non-malignant late effect, or ≥2 late effects was estimated. Standardized mortality ratios (SMR) analyzed the ratio of observed deaths in the study population relative to expected deaths in country, age, race, and sex-matched controls from the general population in the United States and Canada. General population data was obtained from the National Center for Health Statistics.

Cox proportional hazards analysis was used to identify multivariate risk factors for overall mortality, NRM, SMN, and ≥1 late effect. The stepwise selection method with a significance level of 0.05 was used to identify multivariate risk factors. The proportional hazard assumption was checked. If violated, it was included as a time-dependent covariate. Pairwise interaction between significant variables was examined. Separate models were created for patients with HL and those with DLBCL.

The AYA sub-analysis used the same methodology at the main analysis. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient and Transplant Characteristics

Characteristics of the study population are presented in Table 1. Of the 1617 patients eligible for analysis, 836 had cHL 781 had DLBCL. The median duration of follow-up was 127 (range 24–292) months after autoHCT. For cHL patients, the median age at autoHCT was 33 years; 72% (n=606) were included in the AYA group. Forty-four percent (n=371) received radiation therapy prior to autoHCT conditioning and 5% (n=39) received a TBI-based preparative regimen.

For DLBCL patients, the median age at autoHCT was 51 years; 25% (n=192) were included in the AYA group. Twenty-eight percent (n=218) received radiation therapy prior to conditioning and 15% (n=115) received a TBI-based preparative regimen.

Survival and Relapse Outcomes

Figure 1 displays the Kaplan Meier estimates and cumulative incidences of survival outcomes. Among two-year survivors of autoHCT for cHL, OS at 3- and 5-years after autoHCT was 96% (95%CI, 95–98%) and 90% (95%CI, 87–92%). PFS at 3- and 5-years was 93% (95%CI, 91–95%) and 84% (95%CI, 81–86%). The cumulative incidence of relapse was 4% (95%CI, 3–6%) at 3-years and 9% (95%CI, 8–12%) at 5-years after autoHCT. The incidence of NRM was 3% (95%CI, 2–4%) at 3-years and 7% (95%CI, 5–9%) at 5-years.

Of the 256 patients with cHL who died >2 years after autoHCT, relapse accounted for 44% (n=113) of deaths and NRM accounted for 56% (n=143) of deaths. Causes of NRM are presented in Table 2. Of the 173 patients who died >5 years after autoHCT, relapse accounted for 28% (n=49) and NRM accounted for 72% (n=124) of deaths. The SMR was 9.6 (95%CI, 8.1–11.2) for two-year cHL survivors compared to the general population.

Among two-year survivors of autoHCT for DLBCL, OS at 3- and 5-years after autoHCT was 95% (95%CI, 93–96%) and 89% (95%CI, 87–91%). PFS at 3- and 5-years was 91% (95%CI, 89–93%) and 82% (95%CI, 79–85%). The cumulative incidence of relapse was 4% (95%CI, 3–6%) at 3-years and 7% (95%CI, 6–9%) at 5-years after autoHCT. The incidence of NRM was 4% (95%CI, 3–6%) at 3-years and 7% (95%CI, 6–9%) at 5-years.

Of the 223 patients with DLBCL who died >2 years after autoHCT, relapse accounted for 43% (n=96) of deaths and NRM accounted for 57% (n=127) of deaths. Causes of NRM are presented in Table 2. Of the 142 patients who died >5 years after autoHCT, relapse accounted for 29% (n=41) and NRM accounted for 71% (n=101) deaths. The SMR was 3.4 (95% CI, 2.9–4.1) for two-year DLBCL survivors compared to the general population.

Predictors of Mortality

Table 3 displays the multivariate models of overall mortality and NRM in cHL patients. Risk factors for overall mortality included older age (p <.001), male sex (p =0.039), Karnofsky score <90% at the time of autoHCT (p=0.011), TBI-exposure (p <.001), and higher numbers of lines of chemotherapy prior to autoHCT (p=0.015). Predictors of NRM included older age

(p <.0001), Karnofsky score <90% at the time of autoHCT (p=0.011) and TBI-exposure (p <.0001).

Table 4 displays the multivariate models of overall mortality and NRM in DLBCL patients. Risk factors for overall mortality included older age (p <.001) and TBI-exposure (p =0.013). Predictors of NRM were also older age (p <.0001) and TBI-exposure (p=0.043).

Non-Malignant Late Effects

At least one non-malignant late effect was reported in 9% (n=148) of patients. Two or more late effects were reported in 2% (n=30) of patients.

The incidences of specific late effects are described in Table 5. The most frequently reported non-malignant late effects were endocrine impairments, including hypothyroidism (n=50), diabetes (n=23) and gonadal dysfunction (n=16). Cataracts (n=16) and cardiac impairments, including congestive heart failure (n=14) and myocardial infarction (n=11), were the next most commonly reported late effects. Other complications that were reported in ≥10 patients included interstitial pneumonitis/idiopathic pneumonia syndrome (n=12) and stroke/seizures (n=10).

SMN

A total of 105 confirmed SMN occurred ≥2 years post-autoHCT, 44 in cHL and 61 in DLBCL patients. Among cHL patients, biopsy-documented SMN included myelodysplastic/ myeloproliferative syndrome (n=12), genitourinary tract cancers (n=6), acute myeloid leukemia (n=5), gastrointestinal cancer (n=5) and breast cancer (n=5). Predictors of SMN included older age (p <.001) and higher number of lines of chemotherapy (p=0.015, Table 6).

Among DLBCL patients, biopsy-documented SMN included myelodysplastic/ myeloproliferative syndrome (n=24), gastrointestinal (n=7), genitourinary tract cancers (n=7), acute myeloid leukemia (n=5), and breast cancer (n=5). Older age (p <.001) was the only risk factor identified for SMN in DLBCL patients (Table 6).

AYA Sub-analysis

Outcomes of the AYA subpopulation largely mirrored outcomes of the overall population. For cHL, OS was 91% (95%CI, 88–93%), NRM was 7% (95%CI, 5–9%) and relapse was 8% (95%CI, 6–10%) at 5-years after autoHCT. For DLBCL, OS was 97% (95%CI, 94–99%), NRM was 2% (95%CI, 1–5%), and relapse was 5% (95%CI, 2–8%) at 5-years after autoHCT.

Relapse accounted for 47% of deaths in cHL and 31% of deaths in DLBCL. At least one non-malignant late effect was reported in 8% of patients; ≥2 late effects were reported in 1% of the patients. A total of 30 SMN were reported, 25 in cHL and 5 in DLBCL.

For cHL patients, predictors of overall mortality included Karnofsky score <90 (p=0.0004), higher numbers of lines of chemotherapy (p <.0001), and TBI-exposure (p <.0001). Risk factors for NRM included Karnofsky score <90 (p <.0001) and TBI-exposure (p=0.0003).

For DLBCL patients, TBI-exposure (p=0.011) was predictive of late mortality. No significant risk factors were identified for NRM.

Discussion

We present major long-term outcomes, including survival, SMN and late effects, of a multicenter cohort of 1617 two-year autoHCT survivors for cHL or DLBCL treated in a modern era of therapies and reported to the CIBMTR. We found that patients who survived progression-free for ≥2 years after autoHCT had favorable long-term survival. Five years after autoHCT, OS was 90% among cHL and 89% among DLBCL patients. Despite favorable survival outcomes, however, cHL patients had a 9.6-fold increased risk of late mortality and DLBCL patients had a 3.4-fold increased risk of late mortality when compared to an age- and gender-matched general population. Relapse of the primary disease continued to be a major cause of late mortality, accounting for 44% of deaths in cHL patients and 43% of deaths in DLBCL patients. We report a myriad of SMN and non-malignant late effects experienced by survivors. By adjusted analyses, we found that the most consistent risk factors for worse long-term outcomes were TBI-exposure and older age at the time of autoHCT.

The strengths of the study are the representative patient cohort and long follow-up time. The 1617 patients were reported to the CIBMTR from 134 centers in the United States and Canada, representing a range of community and tertiary-care centers from both rural and urban regions. The median follow-up time was 10.6 years, which was longer than comparable studies and allowed for more thorough assessment of mortality and late effects.[9,10,14,18]

In order to focus on treatment-related toxicities of autoHCT, the study population was chosen to represent patients most likely to be cured by transplant – namely the two most common aggressive lymphomas, cHL and *de novo* DLBCL. Despite selecting for patients who survived progression-free for ≥2 years after transplant, relapse remained a major cause of late mortality. Relapse accounted for 44% of deaths among two-year survivors and 29% of deaths among five-year survivors. Consistent with our findings, previous reports have also found relapse to be a leading cause of late deaths among patients who survive the initial post-autoHCT period.[9,10,13,18] This observation highlights the importance of post-transplantation relapse prevention. In this regard, brentuximab vedotin was recently approved as post-transplant consolidation therapy in certain high-risk cHL patients.[19] For DLBCL, while rituximab maintenance was not shown to improve post-transplant disease control, the recently activated BMT CTN IronCLAD trial will examine the role of ibrutinib in ABC type DLBCL.[20] Other agents that warrant investigation as post-transplant relapse prevention strategies include checkpoint inhibitors, immunomodulators, and PI3K inhibitors. Nevertheless, the majority of two- and five-year survivors in the current study did not die due to relapse of their underlying lymphoma. For these patients, the patterns and risk factors for treatment-related morbidity and mortality are most informative.

Similarly to the other large series of long-term outcomes after autoHCT for lymphoma, our study found relatively high rates of SMN.[9,18] This was true despite the lower use of TBI-

containing preparative regimens than was reported in the other, less contemporary studies. The development of SMN is an unfortunate yet inherent late effect of administration of myeloablative therapy. When questioning ways to minimize this risk, perhaps the most important modifiable risk factor identified in this study for impaired overall survival and SMN is the use of TBI. Other reports of SMN after autoHCT for lymphoma did not identify risk factors for the development of SMN.[9,13,15,18] There are, however, conflicting reports about the association of TBI and long-term survival after autoHCT. Worse PFS in patients has been described in patients who received TBI.[18] In contrast, Bhatia, *et al's* large report found that TBI provided a protective effect such that the risk of late death was two-fold higher among patients who did not receive TBI compared with those who did.[9] It should be noted the study captured patients with a range of hematologic malignancies between 1981–1998, thus making the applicability of the TBI findings difficult to compare to the current study.

Our study reported a low incidence of non-malignant late effects; 9% of the cohort had at least one late effect that occurred at least two years after autoHCT and 2% had multiple late effects. Data on late effects after autoHCT for lymphoma are limited, but the few available studies found late effects in the majority of survivors. The largest series reported outcomes of 458 patients who were part of the Bone Marrow Transplant Survivor Study (BMTSS).[21] Of the survivors, 60.7% reported at least one nonmalignant late effect. Notably, data was collected via self-report and the study included patients with different types of hematologic malignancies. A separate analysis that only included patients from the BMTSS cohort who had underwent autoHCT for lymphoma (n=276) also reported high incidences of late effects.[14] For instance, 33%, 23%, and 22% of the study population had neurosensory, endocrine and cardiopulmonary impairments, respectively. The differences in outcomes between the BMTSS analysis and our study would not be explained by differences in follow-up time, as the BMTSS analysis had a median follow-up time of 6 years, compared to 10 years in our study. As the patients in the BMTSS analysis were treated between 1974 and 1998, the majority (69%) received a TBI-based conditioning regimen. This is in contrast to the few patients in the current study treated with TBI-based regimens and may, in part, account for the differences in late effects findings. It is also important to acknowledge that CIBMTR data forms capture a limited number of late effects and screening practices for late effects are not consistent among centers. Therefore, the low incidence of late morbidities in our sample was likely an underrepresentation of the patients' true symptoms burden. Our results, in combination with prior data, support the need for continued long-term follow-up of patients after autoHCT to screen for late effects.[22]

The current study has some limitations that should be considered in interpreting the results. It utilized a retrospective cohort design and specific drug and radiation dosing data were not available. As explained above, only selected late effects data were collected. Furthermore, autoHCT patients are often only followed by their transplant centers for a short time after transplant. Therefore, it can be challenging for centers to ascertain long-term follow up information, which leads to missing data. In addition, we required original biopsy reports to confirm SMN, but were unable to obtain reports from several centers. Hence, we may have underestimated the true incidence of SMN. Though we had a median follow-up time of 10.6 years, it is possible that a longer follow-up time would reveal a larger burden of late effects.

In summary, we found that patients who survived progression-free for at least two years after autoHCT for cHL or DLBCL had favorable long-term outcomes. Five years after autoHCT, 90% of the two-year cHL survivors were alive and 89% of the two-year DLBCL survivors were alive. Survivors, however, continue to be at excess risk for late mortality compared to the general population due to relapse, SMN, and other late effects. Our results affirm the need to build therapies to augment the efficacy of autoHCT and treat relapse after autoHCT. And as outcomes continue to improve, our study highlights the importance of close, systematic follow-up of autoHCT patients to screen for and treat late effects.

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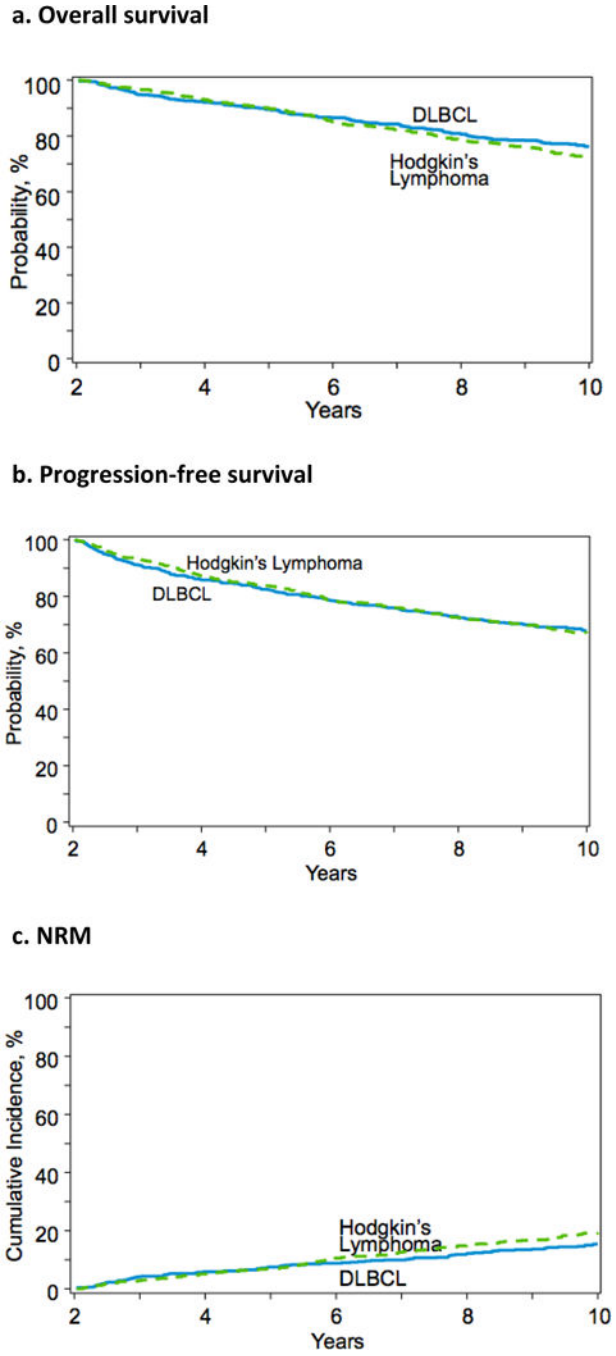

Figure 1.
Survival outcomes among two-year survivors of autoHCT for cHL and DLBCL

Table 1

Patient Characteristics

Variable	cHL N (%)	DLBCL N (%)
Number of patients	836	781
Median age at autoHCT (range), years	33 (15–77)	51 (15–77)
15–19	79 (9)	9 (1)
20–29	274 (33)	66 (8)
30–39	253 (30)	117 (15)
40–49	132 (16)	169 (22)
50–59	66 (8)	213 (27)
60–69	27 (3)	180 (23)
70+	5 (<1)	27 (3)
Sex		
Male	504 (60)	441 (56)
Female	332 (40)	340 (44)
Karnofsky/Lansky score at autoHCT		
<90%	240 (29)	238 (30)
≥90%	575 (69)	509 (65)
Missing	21 (3)	34 (4)
Race/Ethnicity		
Caucasian/White	691 (83)	686 (88)
Other	139 (17)	91 (12)
Unknown/Declined	6 (<1)	4 (<1)
Disease remission status at autoHCT		
Complete response	240 (29)	338 (43)
Partial response	417 (50)	353 (45)
Chemorefractory	77 (9)	57 (7)
Untreated	41 (5)	6 (<1)
Unknown	61 (7)	27 (3)
Extranodal involvement at autoHCT		
No	648 (78)	556 (71)
Yes	158 (19)	429 (55)
Missing	30 (4)	60 (8)
Median (range) interval from diagnosis to autoHCT, months	25 (2–374)	13 (<1–184)
Number of lines of chemotherapy prior to autoHCT conditioning		
1	95 (11)	134 (17)
2	462 (55)	356 (46)
3	196 (23)	196 (25)
4+	65 (8)	60 (8)
Missing	18 (2)	35 (4)
Lines of anthracyclines prior to autoHCT conditioning		
0	37 (4)	28 (4)

Variable	cHL N (%)	DLBCL N (%)
1	621 (74)	599 (77)
≥2	163 (19)	111 (14)
Missing	15 (2)	43 (6)
Lines of bleomycin prior to autoHCT conditioning		
0	116 (14)	652 (83)
1	628 (75)	80 (10)
≥2	81 (10)	8 (1)
Missing	11 (1)	41 (5)
Auto-HCT conditioning regimen		
TBI-based	39 (5)	115 (15)
BuMel/BuCy/Bu+Other	82 (10)	88 (11)
CBV or similar	403 (48)	200 (26)
BEAM or similar	193 (23)	304 (39)
Other	119 (14)	74 (9)
Radiation therapy prior to autoHCT conditioning		
No	299 (36)	373 (48)
Yes	371 (44)	219 (28)
Missing	166 (20)	189 (24)
Stem cell source		
Bone marrow	193 (23)	99 (13)
Peripheral blood	643 (77)	682 (87)
Median follow-up of survivors (range), months	127 (24–292)	121 (24–289)

Table 2

Cause of death for deceased patients who survived progression-free for ≥2 years

Cause of death	**cHL (n=256) N (%)**	**DLBCL (n=223) N (%)**
Relapse	113 (44)	96 (43)
SMN	23 (9)	24 (11)
Organ failure	17 (7)	15 (7)
Infection	7 (3)	13 (6)
Graft rejection (post-allogeneic HCT)	1 (<1)	0
GVHD (post-allogeneic HCT)	2 (1)	0
Other	37 (14)	36 (16)
Unknown	56 (22)	39 (17)

Table 3

Risk factors for overall mortality and NRM in cHL patients

		Overall mortality		NRM	
	N	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**
Age at transplant, years			<.001		<.001
15–39	606	1.00		1.00	
40–54	169	1.31 (0.97–1.76)	0.07	1.27 (0.89–1.81)	0.18
55+	61	2.66 (1.82–3.90)	<.01	2.67 (1.69–4.21)	<.01
Sex[1]			0.039		
Male	504	1.00			
Female	332	0.76 (0.58–0.99)			
Karnofsky score at autoHCT			0.011		0.011
≥90	575	1.00		1.00	
<90	240	1.49 (1.14–1.94)	<.01	1.49 (1.09–2.04)	0.01
Missing	21	1.55 (0.72–3.35)	0.26	2.36 (1.02–5.45)	0.05
Number of lines of chemotherapy			<.001	Not significant	
1	95	1.00			
2	462	0.91 (0.60–1.39)	0.66		
3	196	1.23 (0.78–1.94)	0.37		
4+	65	1.71 (1.01–2.87)	0.04		
Missing	18	2.87 (1.44–5.70)	<.01		
TBI as part of conditioning			<.001		<.001
No	797	1.00		1.00	
Yes	39	2.65 (1.73–4.05)	<.001	2.62 (1.54–4.45)	<.001

Table 4

Risk factors for overall mortality and NRM in DLBCL patients

		Overall mortality		NRM	
	N	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**
Age at transplant, years			<.001		<.001
15–39	192	1.00		1.00	
40–54	277	2.02 (1.32–3.10)	<.01	1.79 (1.08–2.96)	0.02
55+	312	4.23 (2.80–6.39)	<.01	4.22 (2.60–6.85)	<.01
TBI as part of conditioning			0.013		0.043
No	666	1.00		1.00	
Yes	115	1.51 (1.09–2.08)	0.013	1.51 (1.01–2.25)	0.043

Table 5

Incidence of non-malignant late effects occurring ≥2 years after autoHCT

Organ Impairment	Incidence, N (%)
Hypothyroidism	50 (3)
Diabetes	23 (1)
Gonadal dysfunction	16 (<1)
Cataracts	16 (<1)
Congestive heart failure	14 (<1)
Interstitial pneumonitis / idiopathic pneumonia syndrome	12 (<1)
Myocardial infarction	11 (<1)
Stroke/seizures	10 (<1)
Non-infectious liver toxicity	8 (<1)
Renal failure (severe) warranting dialysis	7 (<1)
Avascular necrosis	6 (<1)
Hemorrhagic cystitis	4 (<1)
Thrombotic thrombocytopenic purpura / hemolytic uremic syndrome	4 (<1)
Bronchiolitis obliterans	2 (<1)
Pulmonary hemorrhage	2 (<1)
Pancreatitis	1 (<1)

Table 6

Risk factors for the development of SMN in cHL and DLBCL survivors

	cHL patients			DLBCL patients		
	N	**RR (95% CI)**	**P-value**	**N**	**RR (95% CI)**	**P-value**
Age at transplant, years			<.001			<.001
15–39	570	1.00		182	1.00	
40–54	145	1.54 (0.73–3.25)	0.25	252	3.42 (1.14–10.23)	0.03
55+	52	5.20 (2.38–11.36)	<.01	271	13.56 (4.76–38.63)	<.01
Number of lines of chemotherapy			0.015		Not significant	
1	88	1.00				
2	428	0.95 (0.32–2.84)	0.92			
3	177	2.31 (0.77–6.94)	0.14			
4+	57	2.57 (0.72–9.15)	0.14			
Missing	17	6.36 (1.12–36.01)	0.04			