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Outcomes of Hematopoietic Cell Transplantation for Diffuse Large B Cell Lymphoma Transformed from Follicular Lymphoma

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A B S T R A C T

There are limited data on the outcomes of autologous or allogeneic hematopoietic cell transplantation (HCT) in diffuse large B cell lymphoma transformed from follicular lymphoma. We analyzed transplantation outcomes in 141 subjects with biopsy-proven diffuse large B-cell lymphoma transformed from follicular lymphoma reported to the Center for International Blood and Marrow Transplant Research between 1990 and 2009. Two groups were identified: autologous HCT (auto-HCT; n = 108) and allogeneic HCT (allo-HCT; n = 33). Fewer auto-HCTs were done for transformed follicular lymphoma in 2003 to 2009, with a shift favoring allo-HCT. Auto-HCT was associated with a 1-year nonrelapse mortality (NRM) of 8% (95% confidence interval [CI], 4% to 14%), 5-year progression-free survival of 35% (95% CI, 26% to 45%), and 5-year overall survival of 50% (95% CI, 40% to 59%). In contrast, allo-HCT was associated with a 1-year NRM of 41% (95% CI, 23% to 58%), 5-year progression-free survival of 18% (95% CI, 6% to 35%), and 5-year overall survival of 22% (95% CI, 8% to 41%). Auto-HCT for transformed follicular lymphoma achieves sustained remission in a high proportion of subjects. The high NRM of allo-HCT offset any benefit that might be associated with this transplantation modality.

INTRODUCTION

Follicular lymphoma (FL) is the second most common form of non-Hodgkin lymphoma (NHL) in the Western Hemisphere [1,2]. The histological transformation of FL to diffuse large B-cell lymphoma (DLBCL) occurs in up to 30% of patients at 10 years [3-7]. The rate of such transformed FL (tFL) varies according to the definition of transformation used (ie, whether the definition includes only DLBCL or also Burkitt lymphoma, grade 3B FL, and composite or discordant lymphomas), method of diagnosis (biopsy, cytology, or clinical suspicion), duration of follow-up, and inclusion of autopsy data [8].

Compared with FL, in which the median survival is historically in the 10-year range without a plateau, tFL is usually associated with chemotherapy resistance and shorter survival after chemotherapy [9-13]. There is no standard of care for tFL; therapy for tFL is based mainly on guidelines for de novo advanced DLBCL. Because patients with tFL are typically excluded from FL and DLBCL clinical trials, data on the role of autologous (auto-) or allogeneic (allo-) hematopoietic cell transplantation (HCT) in tFL are limited. Most of the reports published to date are small retrospective studies with brief follow-up [14-20]. Outcomes vary greatly owing to the differing inclusion criteria [14-20]. In addition, most of the studies were conducted before the availability of rituximab, an agent that has improved the outcomes of patients with FL and DLBCL [14-20]. In the present study, we analyzed the outcomes of auto-HCT and allo-HCT for biopsy-proven transformation of FL to DLBCL in a larger patient cohort reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).

METHODS

Data Source

The CIBMTR comprises a voluntary network of more than 500 transplantation centers globally that submit comprehensive data on consecutive autotransplants and allotransplants to a centralized statistical center. The CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. Protected health information during the performance of this observational research is collected and maintained in the CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act (HIPAA). The observational research is conducted with a waiver of informed consent and in compliance with all applicable federal regulations regarding the protection of human research participants as assessed by the Institutional Review Board and the Privacy Officer at the Medical College of Wisconsin. Further information on the data source has been provided by Horowitz [21].

Patient Population

Patients age ≥18 years with FL at diagnosis by the World Health Organization classification [22] with subsequent biopsy-proven histological transformation to DLBCL were included in this study. All pathology reports from the centers were reviewed at the CIBMTR to confirm transformation to DLBCL. Histological transformation to DLBCL was defined as large centroblasts diffusely infiltrating the lymph nodes and effacing the follicular architecture. Cases of composite or discordant lymphoma at diagnosis were not included. Patients with histological transformation of other low-grade lymphomas, such as marginal zone lymphoma and chronic lymphocytic leukemia, were excluded, as were those with transformation to histology other than DLBCL, such as Burkitt lymphoma, lymphoblastic lymphoma, and Hodgkin lymphoma. Patients who had undergone an initial single auto-HCT or allo-HCT for tFL were included, whereas those who had undergone a previous HCT for FL before transformation or after transformation were excluded.

Study Endpoints and Definitions

The main objective of this study was to describe the outcomes of auto-HCT and allo-HCT for patients with DLBCL transformed from FL. The primary endpoint was overall survival (OS), and other endpoints of interest were progression-free survival (PFS), relapse/progression, nonrelapse mortality (NRM), and the incidence of acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD). OS was defined as time to death after transplantation. Death from any cause was considered an event, and surviving patients were censored at the time of last follow-up. PFS was defined as survival without disease relapse or progression after transplantation. Relapse or progression of disease and death were events. Relapse/progression was defined as any new lesion after complete remission or increase in size of previously involved sites after transplantation, with NRM as a competing risk [23]. NRM was defined as any death within the first 28 days after transplantation or any death occurring after day 28 in the absence of disease relapse/progression. Relapse was a competing risk. Those who survived without relapse or progression were censored at last contact for PFS, relapse/progression, and NRM. aGVHD was diagnosed by established criteria [24], as was cGVHD [25]. The intensity of the conditioning regimen was defined based on CIBMTR criteria [26]. Related donor and unrelated donor (URD) transplant recipients were classified based on available HLA typing, as described by Weisdorf et al. [27].

Statistical Methods

Univariate probabilities of OS and PFS for the auto-HCT and allo-HCT cohorts were calculated using the Kaplan-Meier estimator, with the variance estimated using the formula of Greenwood [28]. Variables considered for univariate analysis were age, Karnofsky Performance Status, presence of extranodal disease at transplantation, previous use of rituximab, chemoresistance, interval from diagnosis of FL to transformation, and total body irradiation (TBI)-based conditioning. For allo-HCT, additional variables tested were use of reduced-intensity conditioning (RIC)/nonmyeloablative conditioning (NMAC), antithymocyte globulin (ATG), alemtuzumab, and donor source. Relapse/progression, NRM, and the incidence of aGVHD and cGVHD were estimated using cumulative incidence estimates to accommodate for competing risk.

A Cox proportional hazards regression model was used to identify the risk factors significantly associated with treatment failure (1 − PFS) and overall mortality (1 − OS) for auto-HCT. A multivariate analysis was not considered for allo-HCT, owing to the small size of the study cohort. The variables considered in the multivariate models are listed in Table 2. The assumption of proportional hazards for each factor in the Cox model was tested by adding a time-dependent covariate. The proportionality assumption was satisfied for each factor. A forward and backward stepwise model selection approach was used to identify all significant risk factors.

Table 1
Characteristics of Patients with Transformed DLBCL from FL Who Underwent HCT between 1990 and 2009

Variable	Auto-HCT	Allo-HCT
Number of patients	108	33
Age, yr, median (range)	56 (19-74)	49 (31-66)
Sex, n (%)		
Male	65 (60)	20 (61)
Female	43 (40)	13 (39)
Karnofsky Performance Scale, n (%)		
<90%	35 (32)	8 (24)
90%-100%	68 (63)	25 (76)
Missing	5 (5)	0
Stage at diagnosis, n (%)		
I-II	32 (30)	9 (27)
III-IV	72 (67)	23 (70)
Missing	4 (4)	1 (3)
Disease status before HCT, n (%)		
CR1	9 (8)	2 (6)
CR2	23 (21)	7 (21)
Primary induction failure sensitive	13 (12)	7 (21)
Primary induction failure resistant	3 (3)	3 (10)
Relapsed sensitive	39 (36)	7 (21)
Relapsed resistant	5 (5)	5 (15)
Relapse untreated	5 (5)	1 (3)
Missing*	11 (10)	1 (3)
Chemosensitivity before HCT, n (%)		
Sensitive	90 (83)	23 (70)
Resistant	10 (10)	8 (24)
Untreated/unknown	8 (7)	2 (6)
Lines of chemotherapy before HCT, n (%)		
1-2	33 (31)	7 (21)
≥3	66 (61)	26 (79)
Missing	9 (8)	0
Rituximab exposure between diagnosis and HCT, n (%)		
No	78 (72)	11 (33)
Yes	30 (28)	22 (67)
Known extranodal disease immediately before HCT, n (%)		
No	75 (69)	24 (73)
Yes	28 (26)	9 (27)
Missing	5 (5)	0
Size of involved lymph nodes at HCT, n (%)		
<5 cm	18 (17)	4 (12)
≥5 cm	14 (13)	2 (6)
No lymphadenopathy at HCT	35 (32)	19 (58)
Missing	41 (38)	8 (24)
Interval between diagnosis and HCT, mo, median (range)	54 (6-347)	55 (8-203)
Interval between diagnosis and transformation, mo, median (range)	47 (1-281)	48 (1-173)
Interval between HCT and transformation, mo, median (range)	6 (2-76)	8 (1-31)
Conditioning regimen, n (%)		
Myeloablative	108 (100)	20 (61)
Reduced-intensity		11 (33)
Missing		2 (6)
TBI-based conditioning, n (%)		
No	84 (78)	20 (61)
Yes	24 (22)	12 (36)
Missing	0	1 (3)
Graft type, n (%)		
Bone marrow	16 (15)	10 (30)
Peripheral blood	92 (85)	23 (70)
Use of ATG/alemtuzumab, n (%)		
ATG/alemtuzumab	0	10 (30)
No ATG/alemtuzumab	0	23 (70)
Autologous	108 (100)	0
Type of donor, n (%)		
Matched related donor	0	15 (45)
Matched unrelated donor	0	9 (27)
Other	0	9 (27)
Autologous	108 (100)	0
Year of HCT, n (%)		
1990-1994	32 (30)	1 (3)
1995-2002	51 (47)	9 (27)
2003-2009	25 (23)	23 (70)
Follow-up of survivors, mo, median (range)	85 (3-233)	64 (3-97)

* Chemosensitivity known for 8 cases.

RESULTS

Subject, Disease, and Transplantation-Related Variables

Two groups reported to the CIBMTR between 1990 and 2009 were identified: 108 subjects who underwent auto-HCT and 33 who underwent allo-HCT without a previous auto-HCT (Table 1). Median follow-up in the 2 groups was 85 months and 64 months, respectively. Overall completeness index of the follow-up for the population at 5 years was 89% [29]. The majority of the auto-HCTs were performed between 1990 and 2002, whereas most allo-HCTs were done between 2003 and 2009. The median interval from diagnosis of FL to tFL was 47 months in the auto-HCT group and 48 months in the allo-HCT group. Disease variables at the time of diagnosis of tFL were unavailable. The median interval from diagnosis of FL to transplantation was similar in the 2 groups (54 months versus 55 months), as was the interval from the diagnosis of tFL to transplantation (6 months versus 8 months).

Rituximab was given pretransplantation in 28% of the auto-HCT group and in 61% of the allo-HCT group (Table 1). Radioimmunotherapy with ^{90}Y-ibritumomab tiuxetan or ^{131}I-tositumomab was given to 5 subjects (1 auto-HCT recipient [0.9%] and 4 allo-HCT recipients [12%]). The majority of subjects were responsive to chemotherapy before transplantation in both the auto-HCT group (83%) and the allo-HCT group (70%). However, patients with poor risk features at transplantation were also included in this study. The rate of chemoresistance at transplantation was 10% in the auto-HCT group and 24% in the allo-HCT group. The median number of previous lines of chemotherapy was 3 in the auto-HCT group and 4 in the allo-HCT group, indicating a heavily pretreated cohort. Furthermore, bulky lymphadenopathy of ≥5 cm was present at transplantation in 13% of the auto-HCT recipients and 6% of the allo-HCT recipients, and extranodal disease was present at transplantation in 26% of the auto-HCT group and 27% of the allo-HCT group, indicating a sizeable fraction of patients with poor risk features at transplantation. Cytogenetic data were not available.

In the auto-HCT group, conditioning was provided with a combination of carmustine, etoposide, cytarabine, melphalan (BEAM) in 27% of patients and with cyclophosphamide, carmustine, etoposide (CBV) in 29%. Most allo-HCT recipients (61%) received myeloablative conditioning (MAC) with cyclophosphamide and total body irradiation (Cy/TBI). The remaining subjects reeived RIC/NMAC, primarily with fludarabine and 2 Gy of TBI, fludarabine and cyclophosphamide, or fludarabine and melphalan.

Transplantation Outcomes

The auto-HCT group had a 1 year NRM of 8% (95% confidence interval [CI], 4% to 14%), 5-year probability of relapse/progression of 54% (95% CI, 44% to 63%), 5-year PFS of 35% (95% CI, 26% to 45%), and 5-year OS of 50% (95% CI, 40% to

Table 2
Univariate Survival Analysis for Auto-HCT

Covariate	n	Treatment Failure (1 - PFS)		Overall Mortality (1 - OS)	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
TBI-based conditioning					
No	84	Reference		Reference	
Yes	24	1.27 (0.75-2.14)	.38	1.41 (0.82-2.44)	.22
Chemosensitivity			.38*		.32*
Sensitive	90	Reference		Reference	
Resistant	10	1.89 (0.90-3.97)	.09	1.98 (0.89-4.40)	.09
Time from diagnosis to transformation					
<1 yr	17	Reference		Reference	
≥1 yr	91	0.69 (0.37-1.29)	.25	0.68 (0.35-1.31)	.25
Age					
>60 yr	39	Reference		Reference	
≤60 yr	69	1.06 (0.66-1.72)	.80	1.20 (0.71-2.02)	.50
Karnofsky Performance Status			.50*		.71*
<90%	35	Reference		Reference	
90%-100%	68	0.76 (0.46-1.24)	.27	0.81 (0.48-1.37)	.43
Extranodal disease before HCT			.25*		.66*
No	75	Reference		Reference	
Yes	28	0.95 (0.56-1.60)	.85	0.84 (0.48-1.49)	.55
Rituximab exposure before HCT					
No	78	Reference		Reference	
Yes	30	0.99 (0.59-1.67)	.98	0.65 (0.35-1.20)	.17

* Multiple degree-of-freedom overall test.

59%). The group had a 40-month plateau at 39% (95% CI, 30% to 48%) for PFS and 53% (95% CI, 43% to 63%) for OS (Figure 1). Causes of death included relapse/progression (41%) and second cancers (4%).

The allo-HCT group had a 1-year NRM of 41% (95% CI, 23% to 58%), 5-year probability of relapse/progression of 33% (95% CI, 17% to 50%), 5-year PFS of 18% (95% CI, 6% to 35%), and 5-year OS of 22% (95% CI, 8% to 41%). The cumulative incidences of grade II-IV and grade III-IV aGVHD at day 100 was 42% (95% CI, 26% to 59%) and 27% (95% CI, 14% to 42%), respectively. The cumulative incidence of cGVHD at 1 year was 26% (95% CI, 13% to 43%). The major causes of death were organ failure (24%), relapse/progression (18%), and GVHD (12%). For MAC allo-HCT recipients, the 3-year PFS was 11% (95% CI, 1% to 30%) and 3-year OS was 11% (95% CI, 1% to 29%). For NMAC/RIC allo-HCT recipients, the 3-year PFS was 48% (95% CI, 18% to 79%) and 3-year OS was 67% (95% CI, 35% to 93%). The 1-year NRM for MAC allo-HCT was 57% (95% CI, 31% to 77%). RIC/NMAC allo-HCT recipients did not experience NRM within 5 years, but 5 of the 13 patients (38%) died of relapse/progression.

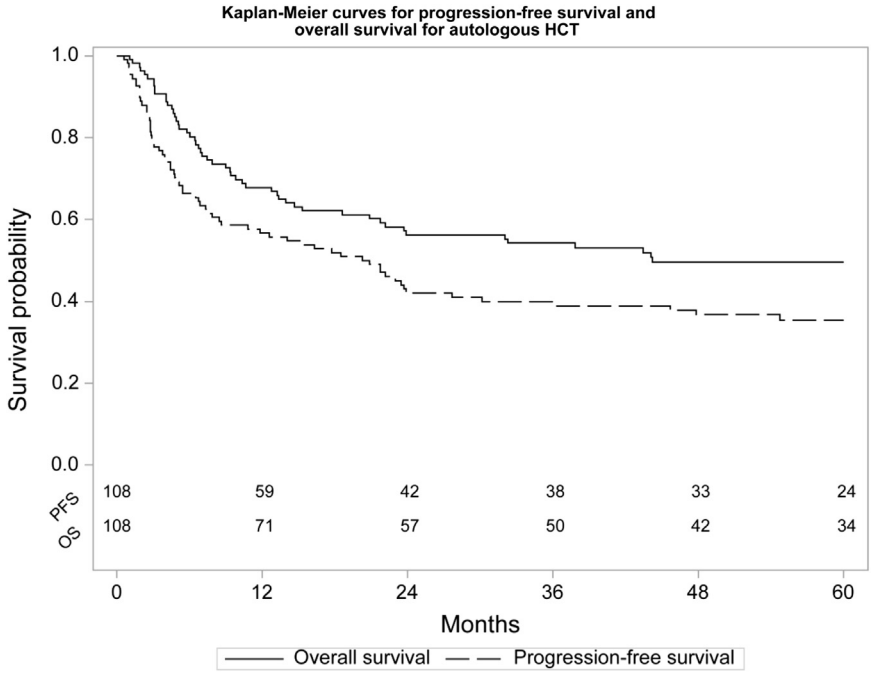

Figure 1. Kaplan-Meier curves for PFS and OS for auto-HCT.

Univariate Analysis

For the auto-HCT group, age, Karnofsky Performance Status, presence of extranodal disease at HCT, pretransplantation rituximab use, time interval from diagnosis of FL to tFL of ≥1 year versus <1 year, chemosensitivity, and TBI conditioning did not have a statistically significant impact on PFS or OS (Table 2). Of note, auto-HCT recipients with chemotherapy-resistant disease achieved a 3 year OS of 27% (95% CI, 7% to 59%) after transplantation.

For the allo-HCT group, age, Karnofsky Performance Status, presence of extranodal disease at HCT, pretransplantation rituximab use, time interval from diagnosis of FL to tFL of ≥1 year versus <1 year, chemosensitivity, use of ATG or alemtuzumab, and donor source did not have a statistically significant impact on PFS or OS (Table 3). Subjects with chemotherapy-resistant disease achieved a 3 year OS of 21% (95% CI, 0 to 62%) after allo-HCT. The 3-year PFS was 11% (95% CI, 1% to 30%) for MAC allo-HCT recipients and 48% (95% CI, 18% to 79%) for RIC/NMAC allo-HCT recipients ($P = .001$), and the 3-year OS was 11% (95% CI, 1% to 29%) for MAC allo-HCT recipients and 67% (95% CI, 35% to 93%) for RIC/NMAC allo-HCT recipients ($P < .001$). RIC/NMAC was associated with significantly higher PFS and OS compared with MAC (Table 3 and Figure 2).

Multivariate Analysis

A Cox proportional hazards regression model was used to identify risk factors significantly associated with treatment failure (1 − PFS) and overall mortality (1 − OS) in the auto-HCT. At a 5% significance level, no risk factors were significant. Multivariate analysis was not considered for allo-HCT, owing to the small size of the study cohort.

DISCUSSION

Our findings indicate that auto-HCT for tFL results in durable remissions in a high proportion of recipients. There was an unexpectedly high NRM in the allo-HCT recipients that might have offset any benefit seen with allo-HCT. It is interesting that clinicians seemingly favored the use of allo-HCT in the 2003 to 2009 period. Given this study's retrospective nature, we cannot discern why clinicians chose auto-HCT or allo-HCT. The pretransplantation variables were comparable in the auto-HCT and allo-HCT groups in terms of risk factors and markers of poor prognosis. Availability of a good donor is not the explanation, given that more than one-half of the patients in both groups did not have a matched sibling. Perhaps the choice reflects a perception that auto-HCT is less effective at producing long-term remission for tFL in the rituximab era. There are limited data on the impact of previous rituximab on outcomes of auto-HCT for tFL [16,30]. We found a 5-year PFS of 35% (95% CI, 26% to 45%) and a 5-year OS of 50% (95% CI, 40% to 59%) after auto-HCT for tFL, with a seemingly similar benefit in those who had previous rituximab therapy. Only 28% of patients received rituximab before auto-HCT, however, and thus firm conclusions regarding the impact of previous rituximab therapy await larger studies. The plateau seen for PFS and OS suggests that a subset of patients may be cured with auto-HCT, although longer follow-up is needed to determine whether these patients remain disease-free.

Table 3
Univariate Survival Analysis for Allo-HCT

Covariate	n	PFS		OS	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
TBI-based conditioning					
No	20	Reference		Reference	
Yes	12	1.07 (0.46-2.49)	.88	0.93 (0.40-2.18)	.87
Chemosensitivity					
Sensitive	23	Reference		Reference	
Resistant	8	1.36 (0.52-3.52)	.53	1.30 (0.50-3.37)	.59
Time from diagnosis to transformation					
<1 yr	9	Reference		Reference	
≥1 yr	24	0.43 (0.18-1.03)	.06	0.53 (0.23-1.25)	.15
Age					
>50 yr	15	Reference		Reference	
≤50 yr	18	0.66 (0.29-1.50)	.32	0.64 (0.28-1.45)	.28
Karnofsky Performance Status					
<90%	8	Reference		Reference	
90%-100%	25	0.88 (0.34-2.24)	.79	0.80 (0.31-2.05)	.64
Extranodal disease before HCT					
No	24	Reference		Reference	
Yes	9	2.21 (0.91-5.37)	.08	2.06 (0.86-4.96)	.11
Rituximab exposure before HCT					
No	11	Reference		Reference	
Yes	22	1.28 (0.52-3.11)	.59	1.40 (0.57-3.40)	.46
ATG/alemtuzumab use					
ATG and/or alemtuzumab	10	Reference		Reference	
No ATG and/or alemtuzumab	23	1.51 (0.59-3.84)	.39	1.66 (0.65-4.23)	.29
Conditioning regimen intensity			.01*		.007*
Myeloablative	20	Reference		Reference	
RIC/NMAC	11	0.16 (0.04-0.54)	.004	0.14 (0.04-0.49)	.002
Disease status at HCT			.24*		.31*
Complete remission	8	Reference		Reference	
Primary induction failure/relapse	21	1.07 (0.38-2.98)	.90	0.90 (0.32-2.52)	.84
Donor type			.53*		.29*
HLA-identical sibling	12	Reference		Reference	
Unrelated donor	18	0.95 (0.39-2.32)	.92	0.82 (0.34-2.01)	.67

* Multiple degree-of-freedom overall test.

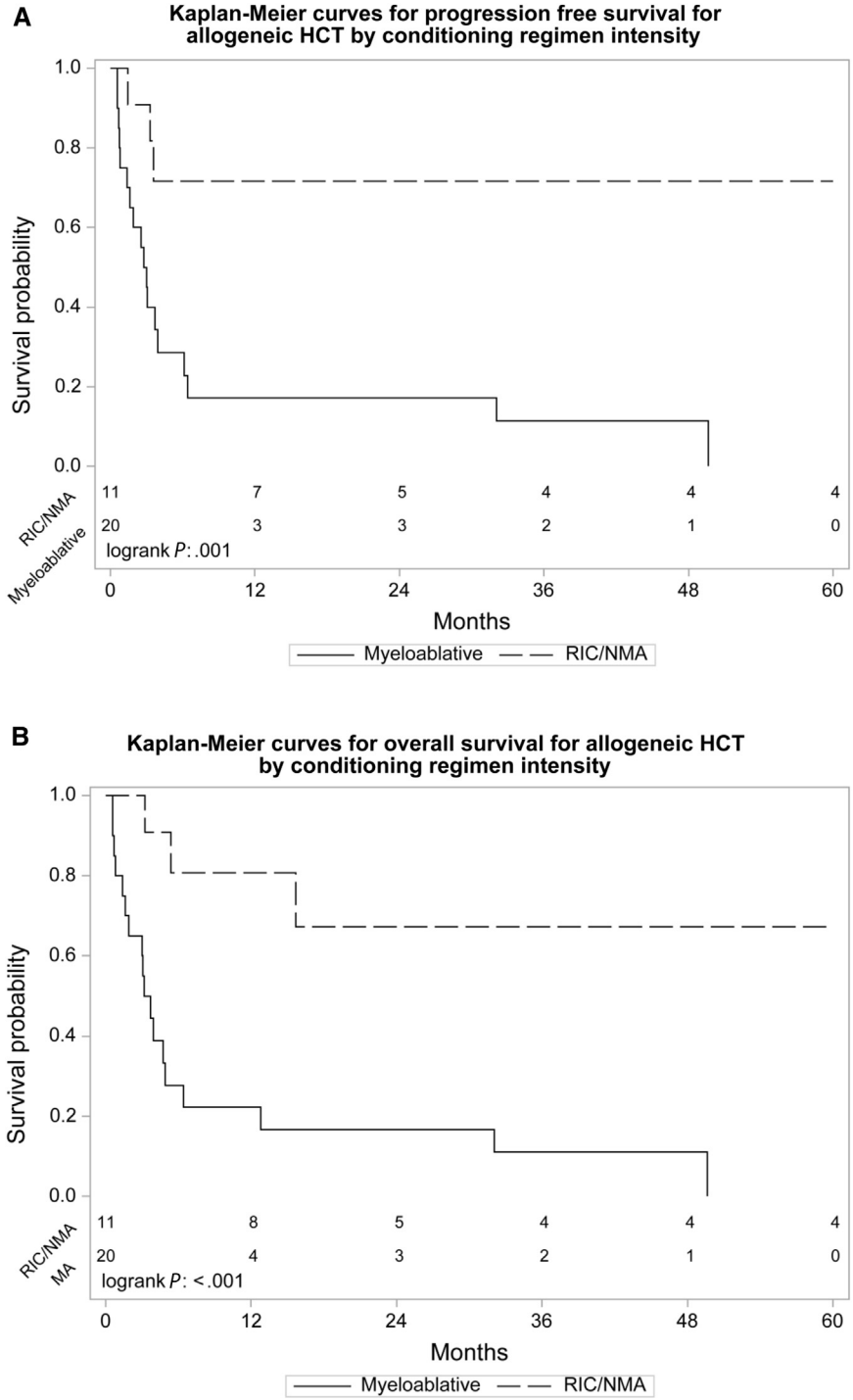

Figure 2. Kaplan-Meier curves for (A) PFS and (B) OS for allo-HCT by conditioning regimen intensity.

Our results are similar to those of the European Bone Marrow Transplant registry report of 50 subjects with tFL from the pre-rituximab era (Table 4) [17]. The sole prospective phase 2 study of patients with tFL, also pre-rituximab, reported a 5-year OS of 47% (95% CI, 29% to 65%) with auto-HCT, which compares favorably with values in transplantation-ineligible patients [31]. More recently, the Canadian Blood and Marrow Transplant Group reported a 5-year OS of 61% (standard error, 7%) with rituximab containing chemotherapy alone without transplantation; however, one-third of this subset of patients had received no therapy for FL before histological transformation, and one-quarter had limited-stage tFL, a highly favorable subset that likely contributed to these results [32]. Even in the pre-rituximab era, watchful waiting before transformation and limited stage of tFL were significant predictors of long-term survival (median survival, 81 months), albeit with a continuous risk of relapse and without a plateau on the survival curve [3,5,33]. In contrast, we found a plateau on the survival curve with auto-HCT in our heavily pretreated cohort. A key limitation to analyses such as ours is

Table 4
Studies on Outcomes of Auto-HCT for tFL

Authors/Type of Study/Years of HCT	n	Patient Age, yr, Median (Range)	TL Definition	PFS	OS	NRM	Comments
Pre-rituximab era							
Williams et al. [17]/EBMT retrospective/1982-1995	50 auto-HCT	45 (28-61)	FL → DLBCL or any high-grade lymphoma	2 yr, 40% 5 yr, 30%	2 yr, 60% 5 yr, 51%	18%	Improved survival if chemosensitive at HCT. Same outcomes for FL, de novo relapsed DLBCL, and transformed lymphoma in matched controlled analysis.
Friedberg et al. [18]/retrospective/1982-1997	27 auto-HCT	44 (29-58)	FL → DLBCL; CLL → DLBCL	5 yr, 46%	5 yr, 58%	0	All relapses after auto-HCT were DLBCL. tFL within 18 mo of diagnosis had better OS.
Eide et al. [31]/prospective, phase 2/1991-2007	30 auto-HCT	55 (31-65)	FL or MZL → DLBCL or between DLBCL and BL, composite lymphoma	5 yr, 32%	5 yr, 47%	7%	Plateau on PFS after 40 mo at 30%.
Rituximab era							
Hamadani et al. [16]/retrospective/1991-2007	24 auto-HCT	56 (47-68)	FL → DLBCL	3 yr, 40%	3 yr, 52%	8%	Improved PFS in 62% of patients with rituximab in treatment course. Chemosensitivity at HCT had no effect on outcomes after HCT.
Ban-Hoefen et al. [30]/retrospective/1998-2010	18 auto-HCT	58 (40-65)	FL or MZL → DLBCL	2 yr, 59%	2 yr, 82%	0	Improved outcomes compared with historical pre-rituximab cohorts [17].
Villa et al. [32]/CBMTG retrospective/2001-2010	97 auto-HCT	56 (32-66)	FL → DLBCL or BL	5 yr, 55%	5 yr, 57%	5%	Auto-HCT had better PFS/OS than rituximab-chemotherapy.
Present study/retrospective/1990-2009	108 auto-HCT	56 (19-74)	FL → DLBCL	5 yr, 36%	5 yr, 50%	8%	No impact of chemosensitivity or previous rituximab use on outcomes.

BL indicates Burkitt lymphoma; MZL, marginal zone lymphoma; EBMT, European Bone Marrow Transplant Registry; CBMTG, Canadian Blood and Marrow Transplant Group; CLL, chronic lymphocytic leukemia; TL, transfomed lymphoma.

Table 5
Studies on Outcomes of Allo-HCT for tFL

Study/n of Patients/Years of HCT	Age, yr, Median (Range)	TL Definition	Median Lines of Chemotherapy before HCT	Conditioning/ Donor	PFS	OS	NRM	Comments
Ramadan et al. [19]/ n = 40/1989- 2005	44 (28-57)	FL, SLL, MZL → intermediate- or higher-grade lymphoma; composite lymphoma	3; chemoresistance, 20%	MAC MRD, 25 URD, 15	5 yr, 23%	5 yr, 23%	3 yr, 36%	No impact on outcomes of composite versus transformed lymphomas or of URD versus MRD. Performance of HCT within 1 yr of diagnosis associated with better outcomes.
Rezvani et al. [20]/n = 62; 16 with TL/1998-2006	54 (33-66)	FL, SLL, MZL → aggressive NHL in 16 patients; remainder had low-grade lymphoma	6; chemoresistance, 23%	NMAC, 2 Gy TBI ± fludarabine MRD, 34 URD, 28	3 yr, 21% for TL 3 yr, 43% for FL	3 yr, 18% for TL 3 yr, 52% for FL	3 yr, 42%	Better outcomes for indolent lymphomas versus transformed lymphoma; no impact of chemoresistance at HCT. 27 patients had previous auto-HCT.
Hamadani et al. [35]/ n = 8/1999-2007	56 (44-63)	FL → DLBCL	4; chemoresistance, 38%	MAC, 6 RIC, 2 MRD, 5 URD, 3	4 yr, 56%	4 yr, 66%	25%	No disease relapse after 1 yr.
Villa et al. [32]/CBMTG/ n = 22/2001-2010	48 (32-57)	FL → DLBCL, BL	3; chemoresistance, 18%	MAC, >95% MRD, 14 URD, 7 MMRD, 1	5 yr, 45%	5 yr, 45%	5 yr, 23%	Two patients had previous auto-HCT for FL. No difference in OS between recipients of allo-HCT and recipients of auto-HCT.
Present study/ n = 33/1990-2009	49 (31-66)	FL → DLBCL	4; chemoresistance, 35%	MAC, 20 RIC/NMAC, 5/6 MRD, 12 URD, 21	5 yr, 18%	5 yr, 22%	1 yr, 41% 5 yr, 49%	No impact of chemoresistance at HCT or URD on outcomes. Better 3-yr PFS/OS with RIC/NMAC compared with MAC (48%/67% versus 11%).

MRD indicates matched related donor; MMRD, mismatched related donor; SLL, small lymphocytic lymphoma; URD, unrelated donor; TL, transformed lymphoma.

that without a prospective comparison, it cannot be proven that auto-HCT is a better approach than nontransplantation therapies. However, the durability of the response is an important advantage of auto-HCT for tFL. Likewise, in the largest study of radioimmunotherapy for tFL, the response rates were high, but durability was poor, with a 5-year PFS of only 17% [34].

In the present study, RIC/NMAC allo-HCT was associated with better PFS and OS compared with MAC allo-HCT (Table 3 and Figure 2). The high NRM after MAC allo-HCT influenced these outcomes and so cannot be recommended. RIC/NMAC allo-HCT may be the best strategy for solving the problem of NRM in allo-HCT, because the low NRM with RIC/NMAC did not obscure the potential benefits of allo-HCT. Firm conclusions about the role of RIC/NMAC allo-HCT in tFL await prospective comparisons with auto-HCT. Nonetheless, outcomes of allo-HCT for tFL appear to be inferior to those of FL. In the study of Khoury et al. [36], NMAC allo-HCT for FL was associated with a 5-year OS of 85% (95% CI, 71% to 93%) with a plateau on the survival curve, implying a curative potential and stronger graft-versus-lymphoma effect. In a recent CIBMTR analysis, GVHD was associated with lower relapse in FL, but not in de novo DLBCL, and this effect was more prominent with RIC than with MAC [37]. Similar to de novo DLBCL, graft-versus-lymphoma effects seem to be less effective in transformed DLBCL than in FL [38].

This study has the limitations of any retrospective study, including inherent patient selection bias as to the type of transplantation performed. The comparison of auto-HCT and allo-HCT is biased, given that most auto-HCTs were performed a decade before the allo-HCTs. Furthermore, the number of allo-HCT recipients is low, and RIC/NMAC was associated with significantly better results compared with MAC, hindering a direct comparison of allo-HCT and auto-HCT. Nonetheless, to the best of our knowledge, this multicenter study is the largest to date that describes transplantation outcomes specifically in biopsy-proven DLBCL transformed from FL. Some previous studies have included heterogeneous low-grade lymphomas transforming to various high-grade lymphomas, all of which can influence transplantation outcomes and make the results difficult to interpret (Tables 4 and 5) [17-20,30-32].

Several conclusions can be drawn from our results. First, RIC/NMAC allo-HCT was associated with better survival compared with MAC allo-HCT, but any potential benefit from MAC was offset by the high NRM. The precise role of allo-HCT awaits prospective comparison of RIC/NMAC allo-HCT and auto-HCT. Second, auto-HCT provides durable survival for tFL irrespective of age, early or late histological transformation, extranodal disease at transplantation, or previous rituximab use. The outcomes of auto-HCT seem to be more durable than published data on nontransplantation therapies, meriting a prospective study to definitively answer this question [7,31-34].

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