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Long-term survival outcomes of reduced-intensity allogeneic or autologous transplantation in relapsed grade 3 follicular lymphoma

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Abstract

Grade-3 follicular lymphoma (FL) has aggressive clinical behavior. To evaluate the optimal first transplantation approach in relapsed/refractory grade-3 FL patients, we compared the long-term outcomes after allogeneic (allo-) vs. autologous hematopoietic cell transplantation (auto-HCT) in the rituximab-era. A total of 197 patients undergoing first RIC allo-HCT or first auto-HCT during 2000-2012 were included. Rituximab-naïve patients were excluded. Allo-HCT recipients were younger; more heavily pretreated, and had a longer interval between diagnosis and HCT. The 5-year probabilities of non-relapse mortality (NRM), relapse/progression, progression-free survival (PFS) and overall survival (OS) for auto-HCT vs. allo-HCT groups were 4% vs. 27% ($p<0.001$); 61% vs. 20% ($p<0.001$); 36% vs. 51% ($p=0.07$) and 59% vs. 54% ($p=0.7$), respectively. On multivariate analysis auto-HCT was associated with reduced risk of NRM (RR=0.20; $p=0.001$). Within the first 11months post-HCT auto- and allo-HCT had similar risks of relapse/progression and PFS. Beyond 11months, auto-HCT was associated with higher risk of relapse/progression (RR=21.3; $p=0.003$) and inferior PFS (RR=3.2; $p=0.005$). In the first 24 months post-HCT, auto-HCT was associated with improved OS (RR=0.42; $p=0.005$), but in long-time survivors (beyond 24 months) it was associated with inferior OS (RR=3.6; $p=0.04$). RIC allo-HCT as the first transplant approach can provide improved PFS and OS, in long-term survivors.

Keywords

grade 3 follicular lymphoma; reduced intensity allo-HCT; auto-HCT; long-time survival

Introduction

Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin lymphoma (NHL), and accounts for 20-30% of all NHL. The WHO classification uses a three-grade system (grades 1-3) in FL, based on the number of centroblasts in 10 neoplastic follicles, expressed per high-power microscopic field.[1] According to this, grade 3 of FL is defined as a tumor with a follicular growth pattern harboring more than 15 centroblasts per high power field by histological examination. This histopathological subtype represents approximately 10-20% of all FL cases. Due to the relative paucity of this lymphoma subtype, the management of grade 3 FL remains an area of controversy.[2-6] Patients with grade 3 FL are often excluded from clinical trials[7] or their outcome are not reported separately in FL studies.[8] In the absence of large prospective studies limited to grade 3 FL, the management of these patients typically follows the diffuse large B-cell lymphoma (DLBCL) guidelines.[9,10]

While both autologous (auto-) and allogeneic hematopoietic cell transplantation (allo-HCT) can provide disease control in relapse/refractory FL[11,12], no study to our knowledge, has assessed the relative efficacy of these two transplantation modalities specifically in grade 3 FL patients. Outcome studies from the pre rituximab-era that lumped grade 3 FL patients with either more indolent grade 1-2 histologies[13,14], or along with more aggressive DLBCL[15] suggest that post HCT outcomes of grade 3 patients are distinct from both indolent and aggressive B-cell lymphoproliferative disorders. These observations underscore the need for specifically reappraising the role of auto- and allo-HCT in relapse/refractory grade 3 FL, in the era of chemoimmunotherapies. We report here, outcomes of patients with grade 3 FL who underwent either a first auto- or first allo-HCT in the rituximab era.

Materials and Methods

Data sources

More than 450 transplantation centers worldwide participating in the CIBMTR contribute data on HCTs to a statistical center at the Medical College of Wisconsin. Participating centers are required to report all HCTs consecutively, with compliance monitored by on-site audits. Patients are followed longitudinally, with yearly follow-up. Computerized checks for discrepancies, physicians' reviews of submitted data, and on-site audits of participating centers ensure data quality. Observational studies by the CIBMTR are performed in compliance with federal regulations with ongoing review by the institutional review board of the Medical College of Wisconsin. All patients provided an informed consent according to the declaration of Helsinki.

Patients

Patients with a histologically proven diagnosis of relapsed/refractory grade 3 follicular lymphoma (FL), undergoing a *first* auto-HCT or a *first* reduced-intensity conditioning/non-myeloablative (RIC/NMA) allo-HCT, reported to the CIBMTR between 2000 and 2012 years, were eligible for inclusion in this study. RIC/NMA allo-HCT recipients with a history of prior auto-HCT were not included, as the primary objective of the study was to assess outcomes of auto- vs. allo-HCT in grade 3 FL, when either modality is used as the first transplantation approach. Donor-source for the allo-HCT cohort was restricted to either HLA-identical siblings or at least a 7/8 (antigen or allele-level) matched unrelated donors (URD). Pediatric patients (<18 years), recipients of alternative donor HCT (e.g. umbilical cord blood, haploidentical, mismatched URD), and patients receiving *ex vivo* graft manipulation (T-cell depleted or CD34 selection) were not included in the analysis. In addition FL patients undergoing histological transformation to DLBCL and those not receiving rituximab-containing therapies before HCT were excluded from this study.

Definitions

The intensity of allo-HCT conditioning regimens was categorized RIC/NMA using established consensus criteria.[16] Previously established criteria[17] for evaluation the degree of HLA matching were used for URD. Complete remission (CR) to last therapy line before HCT on CIBMTR forms is defined as complete resolution of all known disease on radiographic (CAT-scan) assessments, while partial remission (PR) is defined as ≥50%

reduction in the greatest diameter of all sites of known disease and no new sites of disease. Resistant disease is defined as <50% reduction in the diameter of all disease sites, or development of new disease sites. Rituximab resistance was defined as (a) failure to achieve at least a PR to a rituximab-containing therapy line or (b) relapse/progression during or within six months of finishing a rituximab-based therapy.[18]

Study Endpoints

Primary outcomes were non-relapse mortality (NRM), progression/relapse, progression-free survival (PFS) and overall survival (OS). NRM was defined as death without evidence of lymphoma progression/relapse; relapse was considered a competing risk. Progression/relapse was defined as progressive lymphoma after HCT or lymphoma recurrence after a CR; NRM was considered a competing risk. For PFS, a patient was considered a treatment failure at the time of progression/relapse or death from any cause. Patients alive without evidence of disease relapse or progression were censored at last follow-up. The OS was defined as the interval from the date of transplantation to the date of death or last follow-up. Acute GvHD was defined and graded based on the pattern and severity of organ involvement using established criteria.[19] Chronic GvHD was defined as the development of any evidence of chronic GvHD based on clinical criteria.[20] Neutrophil recovery was defined as the first of 3 successive days with absolute neutrophil count (ANC) ≥500/μL after post-transplantation nadir. Platelet recovery was considered to have occurred on the first of three consecutive days with platelet count 20,000/μL or higher, in the absence of platelet transfusion for 7 consecutive days. For neutrophil and platelet recovery, death without the event was considered a competing risk.

Statistical analysis

Adjusted probabilities of PFS and OS were calculated as described previously.[21] Adjusted cumulative incidences of NRM, lymphoma progression/relapse, hematopoietic recovery and second malignancies were calculated to accommodate for competing risks.[22] Patient-, disease- and transplant- related factors were compared between auto-HCT and allo-HCT groups using the Chi-square test for categorical variables and the Wilcoxon sample test for continuous variables. Associations among patient-, disease, and transplantation-related variables and outcomes of interest were evaluated using Cox proportional hazards regression. Backward elimination was used to identify covariates that influenced outcomes. Covariates with a $p<0.05$ were considered significant. The proportional hazards assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome. Covariates violating the proportional hazards assumption were added as time-dependent covariates in the Cox regression model. Interactions between the main effect and significant covariates were examined. Results are expressed as relative risk (RR). All analyses were performed using SAS 9.3. The variables considered in multivariate analysis are shown in Table 1S of supplemental appendix.

Results

Patients

A total of 197 patients with relapsed or refractory grade 3 FL undergoing a first auto-HCT (n=136) or a first RIC allo-HCT (n=61) between 2000 and 2012 years, were identified who fulfilled the inclusion criteria. Patient-, disease- and transplant-related characteristics are detailed in Table 1. Patients receiving allografts were younger, more heavily pretreated, and had a longer interval between diagnosis and HCT. More auto-HCT recipients had a history of previous doxorubicin-based chemotherapies. The frequency of chemotherapy- and rituximab-resistance before HCT did not differ between both groups. There was no significant difference in the duration of remission following first-line therapy between the two transplant groups. BEAM (carmustine, etoposide, cytarabine, melphalan) and CBV (cyclophosphamide, carmustine and etoposide) were the most common conditioning regimens for auto-HCT. Fludarabine in combination with an alkylating agent was the most common RIC approach in the allo-HCT cohort. Eight auto-HCT patients and 13 allo-HCT patients received total body irradiation (TBI)-based conditioning regimens. Five patients each in allo-HCT group received antithymocyte globulin and alemtuzumab with conditioning.

Rates of engraftment and GvHD

Neutrophil and platelet engraftment was similar in the auto- and allo-HCT groups (Table 2). The cumulative incidence of acute GvHD (grade II-IV) at day +100 was 25% (95%CI: 15-36%). The cumulative incidence of chronic GvHD at 5 years post-transplant was 55% (95%CI: 40-71%). In the allo-HCT group, GvHD was the most frequent cause of death, as opposed to relapsed FL in the auto-HCT cohort (Table 2S in Supplemental Appendix).

Non-relapse mortality

Seventeen patients in the allo-HCT group and 7 in the auto-HCT group experienced NRM (Table 2S in the Supplemental Appendix). The adjusted probability of NRM at 5 years was significantly higher in the allo-HCT group (27% vs. 4%; $p<0.001$) (Table 2; Figure 1a). On multivariate analysis, auto-HCT (relative risk [RR]=0.20, 95%CI: 0.08-0.50; p=0.0006) and TBI-free conditioning regimens (RR=0.33, p=0.02) were associated with a lower risk of NRM, while a low Karnofsky performance score (KPS) <90 (RR=3.12; p=0.01) was associated with a higher NRM risk (Table 3).

Disease progression/relapse

The adjusted probability of disease progression/relapse at 5 years was significantly higher in the auto-HCT group as compared to the allo-HCT group (61% vs. 20%; $p<0.001$) (Table 2, Figure 1b). In multivariate models, the main effect (auto-vs. allo-HCT) displayed a time-varying effect on the risk of lymphoma progression/relapse. During the first 11 months after HCT no significant difference was seen between the two groups in terms of risk of progression/relapse (RR=1.62, 95%CI: 0.86-3.03; p=0.13). Beyond 11 months, auto-HCT was associated with a significantly higher risk of progression/relapse (RR=21.33, 95%CI: 2.90-157.08; p=0.003). Other factors associated with reduced risk of progression/relapse

included female sex (RR=0.63, 95% CI: 0.41-0.98, p=0.04) and no history of radiation therapy prior to HCT (RR=0.58; 95% CI: 0.36-0.95, p=0.03). Patients with chemorefractory disease experienced increased risk of progression/relpase (RR=3.13; 95% CI: 1.65-5.93, p=0.0005).

One patient in the allo-HCT group received post HCT maintenance with rituximab, while 11 patients in the auto-HCT group received rituximab maintenance and 1 patient received interferon maintenance. Sixteen (12%) auto-HCT patients after experience disease progression or relapse underwent subsequent allo-HCT.

Progression-free survival

The adjusted probability of 5-year PFS did not differ significantly following allo-HCT as compared to auto-HCT (51% vs. 36%; p=0.07) (Table 2, Figure 1c). On multivariate analysis, the main effect (auto-HCT vs. allo-HCT) displayed a time-varying effect on the risk of treatment failure. During the first 11 months post-HCT, no significant difference was seen between the two groups in terms of risk of treatment failure (RR=0.87, 95%CI: 0.52-1.45; p=0.59). But beyond 11 months, auto-HCT was associated with a significantly higher risk of treatment failure (i.e. inferior PFS) (RR=3.24, 95%CI: 1.44-7.30; p=0.005). The chemosensitive disease was predictive of improved PFS in the whole cohort (Table 3).

Overall survival

The median follow-up in the allo- and auto-HCT groups was 57 months (range 5-132) and 59 months (range 3-145), respectively. The 5-year adjusted probability of OS for the auto-HCT and allo-HCT groups was 59% and 54%, respectively (p=0.70) (Table 2; Figure 1d). On multivariate analysis, within the first 24 months after transplantation, auto-HCT was associated with a reduced risk of mortality (i.e. improved OS) (RR=0.43; 95%CI: 0.24-0.78; p=0.005). In contrast, beyond 24 months, auto-HCT was associated with a higher risk for mortality (i.e. inferior OS) (RR=3.59; 95%CI: 1.05-12.22; p=0.04). Other factors positively impacting on OS in the whole cohort were younger age (<60 years) and chemosensitive disease before HCT (Table 3).

Secondary malignancies

The 5 year cumulative incidence rates of second malignancies did not differ significantly between both cohorts (allo-HCT=8%, auto-HCT=9%; p=0.53) (Table 2). The details of the second malignancies are summarized in Table 3S of the supplemental appendix. Non-melanoma skin cancers were the most frequent second malignancy type in the allo-HCT group. Secondary hematological malignancies were only seen in the auto-HCT cohort (n=4). Four patients (accounting for 7% of mortality post auto-HCT) in the auto-group but none of the patients from allo-HCT group died because of a secondary malignancy (Table 2S).

Discussion

The relative benefits of auto- vs. allo-HCT in the biologically distinct subgroup of grade 3 FL patients have not been analyzed separately, to date.[11,12,23] In the current CIBMTR analysis we aimed to assess the role of auto- vs. allo-HCT as the first transplantation strategy

in rituximab-treated cohort of grade 3 FL, and made several observations: First, allo-HCT remains associated with higher NRM. Second, disease relapse beyond one year post allo-HCT was rare, while late relapses were frequent following auto-HCT. Third risk of second hematological malignancies was confined to the auto-HCT cohort. Fourth, allo-HCT was associated with improved late survival outcomes.

The management of grade 3 FL is controversial. Some investigators treat grade 3a histology as FL, while others approach it as DLBCL. Despite the unique biology of grade 3b histology[6], the distinction between FL grade 3a and 3b, to date has not been shown to have clinical significance, conclusively. The National Comprehensive Cancer Network recommends treating grade 3 FL according DLBCL guidelines, without making a distinction between grades 3a vs. 3b.[9] These guidelines are reflective of available literature where except one notable exception[24], the majority of published experience suggests neither any difference in outcomes of grade 3a vs. 3b subtypes nor any added benefit of anthracycline-based therapies in grade 3b patients.[25-28] CIBMTR forms prior to 2013 did not collect information regarding grade 3a vs. 3b histology and the current analysis cannot to address whether this distinction has any bearing on HCT outcomes. In addition, while patients with transformed DLBCL were excluded, assignment to grade 3 histology in CIBMTR registry is according to data reported by transplant centers, without a central histopathological review. While acknowledging this limitation, it is also important to highlight that CIBMTR systematically conducts onsite data audits at individual transplant centers to ensure quality and accuracy of data reported the registry.

The frequent inclusion of grade 3 FL with the more indolent or aggressive lymphomas undergoing auto-[13,14] or allo-HCT[15] has meant that the relative benefits of these two transplantation modalities in this unique subset of FL remains unknown. In the pre-rituximab era, Pham et al.[13] observed no significant impact of grade 3 histology on survival outcomes of FL patients (grade 3, n=38, 17% of the whole cohort) after auto-HCT. In contrast, Vose et al.[14] found grade 3 histology to be associated with increased risk of treatment failure (RR 1.97, p=0.004), progression (RR 2.14, p=0.006) and worse survival outcomes after auto-HCT. In the context of allo-HCT, CIBMTR[15] reported on 533 patients with refractory aggressive lymphomas, including 80 patients with (15%) grade 3 FL, undergoing allo-HCT. Interestingly, the authors found a positive prognostic impact of grade 3 histology on survival outcomes (RR 0.53, p<0.001) compared to DLBCL, underscoring the differential post transplantation course of grade 3 FL, compared to more aggressive histologies.

A graft-*versus*-Lymphoma (GvL) effect had been suggested for patients with indolent lymphomas based on plateau in post HCT PFS[29-33] and on observed responses following withdrawal of immunosuppression and donor lymphocyte infusions.[31,33] In our current study, disease relapses 1-year after allo-HCT are virtually absent (Table 2), compared to continued risk of relapse following auto-HCT, potentially reflecting clinically relevant GvL effects in grade 3 FL. With the limitations of our registry analysis and sample size in mind, after adjusting for significant covariates, multivariate models in our study suggest that, while in the early post HCT period both transplantation approaches provide comparable survival outcomes, long-term survivors (beyond 2 years) of allo-HCT may enjoy a late PFS and OS

benefit. In addition, multivariate models in the current study also identify several clinically relevant modifiable and non-modifiable factors impacting transplantation outcomes. Poor performance score and advancing recipient age were predictors of NRM and OS (Table 3), underscoring the importance of careful patient selection in determining HCT outcomes. Despite, restricting the current study to RIC allografts, TBI in conditioning was associated with higher NRM and overall mortality, suggesting that even within the context lower-intensity transplants, the type and composition of preparative regimen remains a modifiable factor capable of impacting transplantation outcomes.

We also carefully evaluated the rates of second malignancies after both transplant approaches. Histopathological reports of all second cancers were obtained from the transplantation centers and reviewed for accuracy. In the published literature, second malignancies are observed in 5-20% of lymphoma patients after auto-[11,34–36] and in 2-6% of patients after allo-HCT.[37,38] In the current analysis we found no significant difference in the cumulative incidence of all second malignancies between auto- and allo-HCT cohorts (Table 2); however, second hematological malignancies were confined to the auto-HCT group (Table 3S). The most frequent second cancers in allo-group were non-melanoma skin cancers, a potential curable malignancy in majority of cases. Second cancers accounted for 7% of the mortality following autografting, and none of the patients undergoing allo-HCT died because of a second cancer.

The application of the findings from the current analysis into clinical practice warrants consideration of certain key facts. The current registry study does not represent a decision analysis designed to guide selection of one transplant modality over another, at a certain post in a grade 3 FL patient's disease course. The choice of either transplantation modality for any given patient in our data set reflects a complex interplay of several factors including; transplant center's practice/preference, patient age, donor availability and presence of medical comorbidities, among others. With these limitations in mind, the current study provides, hitherto unpublished data to aid clinical decision making. Collectively our data indicate that in relapsed/refractory grade 3 FL, either auto- or allo-HCT when applied as the first transplantation modality can provide durable disease control. Hence the choice of first transplantation modality, in current era should take into account several practical considerations. The potential benefits of auto-HCT including disease control with relatively low morbidity and NRM, should be carefully weighed against the continued risk of disease relapse and higher risk of second hematological malignancies following this procedure. On the other hand, early NRM and quality-of-life considerations (often secondary to GvHD) remain a limitation of allo-HCT. Having said that, disease relapses 1-year after allo-HCT in our study were rare (Figure 1b), and patients who are able to survive the initial procedure-related toxicities, appear to have improved long term survival outcomes. Based on our data derived from chemoimmunotherapy treated grade 3 FL, selecting auto-HCT as first transplant modality in less fit, or elderly FL patients, or those without eligible donors, relatively earlier in the disease course appears reasonable. In carefully selected individuals, allo-HCT potentially later in the disease course can provide (at least) comparable survival outcomes, with substantially reduced risk of therapy failure.

In conclusion, our study shows that in grade 3 FL patients treated with contemporary rituximab-based chemoimmunotherapies, RIC allo-HCT when compared to auto-HCT is associated with higher NRM, but significantly reduced risk of disease relapse and potentially improved survival outcomes in a subset of long-term survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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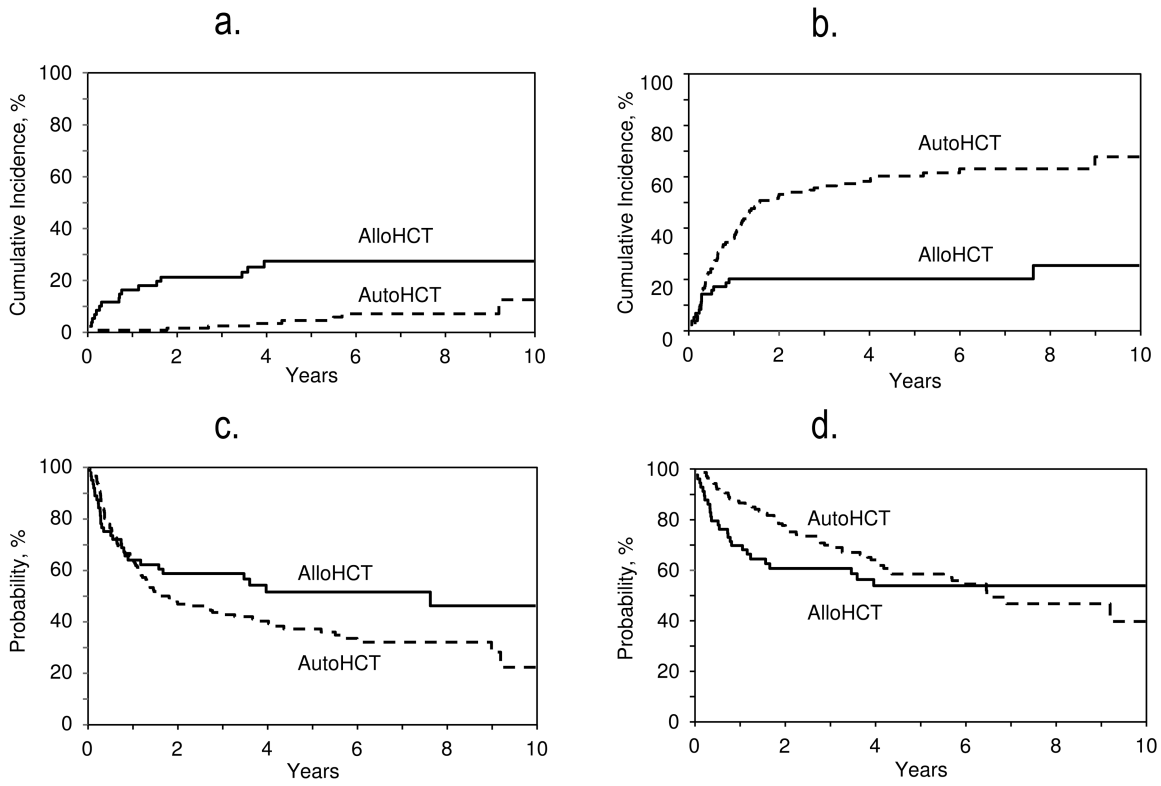

Figure 1.

Adjusted probabilities for NRM (5 years; auto-HCT, n=135; allo-HCT, n=61; p<0.001) [Figure 1a]. Adjusted probabilities for relapse (5 years; n=135; allo-HCT, n=61; p<0.001) [Figure 1b]. Adjusted probabilities for PFS (5 years; n=135; allo-HCT, n=61; p=0.07) [Figure 1c] Adjusted probabilities for OS (5 years; n=136; allo-HCT, n=61; p=0.7) [Figure 1d]

Table 1

Characteristics of patients who underwent auto- or allo-HCT for non- transformed relapsed/refractory follicular lymphoma grade 3 from 2000-2012 reported to the CIBMTR

Variable	Allo-HCT	Auto-HCT	P-value
Number of patients	**61**	**136**	
Age at transplant, years			0.006
Median	53 (36-64)	57 (27-76)	
Male gender	41 (67)	79 (58)	0.22
Karnofsky Performance Score			0.21
<90%	18 (30)	39 (29)	
90-100%	42 (69)	86 (63)	
Missing	1 (2)	11 (8)	
Race			0.81
Caucasian/White	54 (89)	121 (89)	
Black	2 (3)	8 (6)	
Others	5 (8)	7 (5)	
Disease stage at diagnosis			0.11
I-II	8 (13)	25 (18)	
III-IV	52 (85)	105 (77)	
Unknown	1 (2)	6 (4)	
Time from diagnosis to transplant, months	32 (5-159)	24 (6-224)	0.02
B Symptoms at diagnosis	24 (39)	36 (26)	0.14
Elevated LDH concentration at transplant	17 (28)	53 (39)	0.23
Unknown	7 (11)	18 (13)	
Bulky disease at diagnosis	7 (11)	16 (12)	0.99
Bone marrow involved with FL at HCT	6 (10)	3 (2)	0.02
Missing	52 (85)	115 (85)	
Extranodal involvement at transplant	10 (16)	23 (17)	0.86
Missing	1 (2)	4 (3)	
Rituximab-resistant	30 (49)	84 (62)	0.12
Not evaluable	3 (5)	10 (7)	
Median/Mean chemotherapy lines (range)	3/3.3 (1-5)	3/2.9 (1-5)	0.01
Duration of first-line therapy response			0.31
<1 year	22 (36)	44 (32)	
≥1 year	34 (56)	87 (64)	
Missing	5 (8)	5 (4)	
History of radiation therapy before HCT	10 (16)	26 (19)	0.65
History of doxorubicin-based therapies	49 (80)	125 (92)	0.02
Disease response at transplant			0.07
CR	22 (36)	43 (32)	
PR	27 (44)	80 (59)	

Variable	Allo-HCT	Auto-HCT	P-value
Number of patients	**61**	**136**	
Chemoresistant/untreated relapse	12 (20)	13 (10)	
Type of donor		N/A	N/A
HLA-identical sibling	36 (59)		
Unrelated well-matched *(8/8 allele level)*	23 (38)		
Unrelated partially matched *(7/8 antigen level or 7/8 allele level)*	2 (3)		
TBI-based conditioning	9 (15)	8 (6)	0.04
Conditioning regimens (AlloHCT) ***		N/A	N/A
Fludarabine/Busulfan ±TBI	7 (11)		
Fludarabine/Melphalan ±TBI	14 (23)		
BEAM and similar	4 (7)		
2Gy TBI ± Fludarabine	6 (10)		
Fludarabine/Cyclophosphamide	21 (34)		
CBV	3 (5)		
Others[a]	6 (10)		
Conditioning regimens (AutoHCT)	N/A		N/A
TBI-based ****		8 (6)	
BEAM and similar		99 (73)	
CBV or similar		20 (15)	
BuMEL/BuCy		5 (4)	
Others *		4 (3)	
Graft type			
Bone marrow	3 (5)	1 (1)	0.05
Peripheral blood	58 (95)	135 (99)	
GVHD prophylaxis		N/A	N/A
Tacrolimus-based	33 (54)		
Cyclosporine-based	24 (39)		
Others **	4 (7)		
ATG or alemtuzumab used	10 (16)	N/A	N/A
Median follow up of survivors, months	57 (5-132)	59 (3-145)	

Abbreviations: BEAM=carmustine, etoposide, cytarabine, melphalan; CBV = cyclophosphamide, BCNU and etoposide; CR = complete remission; GVHD = graft *versus* host disease; N/A=not applicable.

[a]TBI+pantostatin (n=1), melphalan+cyclophosphamide (n=1), busulfan alone (n=1), busulfan+cyclophosphamide (n=1), busulfan +cyclophosphamide+etoposide (n=1), TBI+busulfan+cytarabine (n=1).

*Carboplatin+mitoxanthron+thiotepa (n=1), carboplatin+thiotepa+etoposide (n=1), melphalan alone (n=1) and nitro alone (n=1).

**Other GVHD prophylaxis: not specified (n=4).

***TBI doses for allo-HCT patients 400cGy=1, 600cGy=1, 200cGy=7, missing=4

****TBI doses for auto-HCT patients 1000cGy=1, 1200cGy=6, 1320=1

Table 2

Univariate analysis for patients with grade 3 follicular lymphoma.

	Allo-HCT (N = 61)		Auto-HCT (N = 136)		P-value
Outcomes	**N**	**Prob (95% CI)**	**N**	**Prob (95% CI)**	
ANC recovery >0.5 × 10^9/L					
28-day		100 (87-100)%		100 (93-100)	0.99
100-day		100 (87-100)%		100 (93-100)%	0.99
Platelet recovery ≥ 20 × 10^9	42		68		
28-day		83 (67-92)%		82 (71-90)%	0.90
100-day		88 (72-95)%		96 (86-99)%	0.22
Acute GVHD (II-IV)	61			N/A	
100-day		25 (15-36)%			
Chronic GVHD	60			N/A	
1-year		47 (34-59)%			
3-year		53 (38-68)%			
5-year		55 (40-71)%			
New malignancy	59		128		
1-year		3 (0-8)%		1 (0-4)%	0.52
3-year		6 (2-15)%		6 (3-12)%	0.992
5-year		8 (2-15)%		9 (4-16)%	0.533
Adjusted probabilities					
NRM	61		135		
1-year		16 (7-25)%		0 (0-0)%	<0.001
3-year		21 (11-31)%		2 (0-4)%	<0.001
5-year		27 (17-38)%		4 (0-8)%	<0.001
Relapse/Progression	61		135		
1-year		20 (10-29)%		36 (28-44)%	0.010
3-year		20 (10-29)%		56 (48-64)%	<0.001
5-year		20 (10-29)%		61 (53-69)%	<0.001
PFS	61		135		
1-year		63 (52-75)%		64 (56-72)%	0.883

Outcomes	Allo-HCT (N = 61) N	Allo-HCT (N = 61) Prob (95% CI)	Auto-HCT (N = 136) N	Auto-HCT (N = 136) Prob (95% CI)	P-value
3-year		58 (46-70)%		42 (34-51)%	0.04
5-year		51 (37-64)%		36 (27-44)%	0.066
Overall survival	61		136		
1-year		70 (58-81)%		87 (81-93)%	0.79
3-year		61 (48-73)%		70 (62-78)%	0.22
5-year		54 (40-67)%		59 (50-68)%	0.70

Abbreviations: ANC = neutrophil recovery; NRM= non-relapse mortality; PFS = progression-free survival; PROB = probability; CI = confidence interval; NA = not applicable; NE = not evaluable

Probabilities of neutrophil and platelet recovery, platelet recovery, acute GVHD, chronic GVHD, treatment-related mortality and progression/relapse were calculated using the cumulative incidence estimate. Progression-free survival and overall survival was calculated using the Kaplan-Meier product limit estimate.

* Log-rank test

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Table 3

Multivariate analysis for grade 3 follicular lymphoma patients.

Variable	N	RR	95% CI Lower Limit	95% CI Upper Limit	P-value
Non-relapse mortality					
Main effect					
Allo-HCT	61	1			
Auto-HCT	135	0.202	0.082	0.501	0.0006
KPS					
≥90%	127	1			
<90%	57	3.124	1.328	7.351	0.0091
Missing	12	2.178	0.26	18.221	0.4727
TBI					
Yes	16	1			
No	180	0.327	0.126	0.849	0.0216
Progression/Relapse					
Main effect (≤ 11 months)					
Allo-HCT	61	1			
Auto-HCT	135	1.615	0.863	3.025	0.1341
Main effect (> 11 months)					
Allo-HCT	36	1			
Auto-HCT	87	21.329	2.896	157.075	0.0027
Sex					
Male	119	1			
Female	77	0.632	0.408	0.979	0.04
Chemosensitivity at HCT					
CR	65	1			
PR	106	1.322	0.817	2.14	0.2559
Chemoresistant/untreated	25	3.13	1.653	5.925	0.0005
Prior radiotherapy					
Yes	36	1			

Variable	N	RR	95% CI Lower Limit	95% CI Upper Limit	P-value
No	160	0.584	0.359	0.951	0.0307
Progression-free survival					
Main effect					
Allo-HCT	61	1			
Auto-HCT	135	0.869	0.521	1.448	0.5892
Main effect (> 11 months)					
Allo-HCT	36	1			
Auto-HCT	87	3.238	1.437	7.295	0.0046
Chemosensitivity at HCT					
CR	65	1			
PR	106	1.4	0.915	2.144	0.1214
Chemoresistant/untreated	25	2.835	1.606	5.004	0.0003
Overall survival					
Main effect (≤24 months)					
Allo-HCT	61	1			
Auto-HCT	136	0.427	0.235	0.776	0.0052
Main effect (>24 months)					
Allo-HCT	32	1			
Auto-HCT	95	3.587	1.053	12.217	0.041
Age					
< 40	11	1			
40-49	45	3.173	0.724	13.917	0.1258
50-59	80	2.601	0.609	11.114	0.1972
≥60	61	5.374	1.253	23.052	0.0236
Chemosensitivity at HCT					
CR	65	1			
PR	107	1.271	0.762	2.122	0.3584
Chemoresistant/untreated	25	2.674	1.388	5.152	0.0033
TBI					

Variable	N	RR	95% CI Lower Limit	95% CI Upper Limit	P-value
Yes	17	1			
No	180	0.443	0.22	0.895	0.0232

Abbreviations: N = number of patints; RR=relative risk; KPS= Karnosfky performance status; TBI=total body irradiation; CR= complete remission; PR=partial remission; CI = confidence interval.