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CORRESPONDENCE

Risk factors and outcomes of follicular lymphoma after allogeneic hematopoietic stem cell transplantation using HLA-matched sibling, unrelated, and haploidentical-related donors

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To the Editor:

Recent studies investigated the outcomes of patients with relapsed/refractory (R/R) follicular lymphoma (FL) undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1, 2]. Risk factors for progression-free survival (PFS) such as age [1–4], number of chemotherapy regimens [2], chemosensitivity or response before ASCT [1–5], performance status [2], and extranodal involvement [4] have been reported, but not consistently, across studies. Also, data on head-to-head comparisons according to different donor types are lacking. The aims of the study were to evaluate long-term outcomes, identify prognostic factors for PFS, and provide data comparing MSD, MUD, and haploidentical donors in 194 patients with R/R FL who underwent allo-HSCT.

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Patients with R/R grades 1-3b FL who underwent first allo-HSCT from a MSD, MUD, or haploidentical donor from January 2000 to December 2018 reported to GETH were included. Patients with transformed FL, syngeneic donor, cord blood or mismatched unrelated donor, and ex vivo T cell-depleted grafts were excluded. Chi-square test was used to compare categorical variables and the Wilcoxon test for continuous variables. The probability of acute and chronic GVHD, NRM, and relapse was calculated using the method of cumulative incidence [6, 7]. Unadjusted time-to-event analyses were performed using the Kaplan–Meier estimate [8], and, for comparisons, the log-rank tests [9]. A Cox proportional hazards model or the Fine and Gray method for competing events were used for multivariable analysis [6]. Statistical analyses were performed using R and SPSS.

Patient, disease, and transplant characteristics according to the donor type are summarized in Table 1.

The cumulative incidence of grade II–IV and III–IV aGVHD at 274 days after transplantation was 48% (95% CI,41–55%) and 20% (95% CI, 14–26%), respectively. The 3-year cumulative incidence of cGVHD and extensive cGVHD was 40% (95% CI, 33–47%) and 21% (95% CI, 16–27%), respectively.

The cumulative incidence of NRM at 100 days, 1 year, and 9 years was 12% (95% CI, 7–16%), 27% (95% CI, 21–33%), and 39% (95% CI, 31–46%), respectively. The causes of NRM were GVHD ($n = 27$), infections ($n = 24$), secondary malignancies ($n = 7$), SOS ($n = 4$), others ($n = 10$), and unknown causes ($n = 5$). Variables associated with increased NRM were: age at transplant >50 (hazard ratio (HR) 2.3, 95% CI, 1.3–4, $P = 0.002$), >3 prior therapy lines (HR 1.8, 95% CI, 1.1–3, $P = 0.01$), high HCT-CI (HR 1.8, 95% CI, 1.1–3.2, $P = 0.03$), and grade III–IV aGVHD (HR 4.3, 95% CI, 2.5–7.5, $P < 0.001$). Based on pretransplant risk factors, four groups with different NRM cumulative incidences at 3 years are differentiated: 16% (95% CI, 7–26%) with 0, 29% (95% CI, 19–40%) with 1, 52% (95% CI, 38–65%) with 2 and 79% (95% CI, 44–100%) with all 3 risk factors at 3 years ($P < 0.001$).

The cumulative incidence of progression/relapse at 9 years was 8% (95% CI, 4–12). The overall PFS, OS, and GRFS at 9-year was 53% (95% CI, 46–61%), 58% (95% CI, 51–66%), and 36% (95% CI,29–43%), respectively.

In multivariable analysis, not achieving complete remission (CR) prior to allo-HSCT (HR 1.7, 95% CI, 1.1–2.7, $P = 0.02$), age >50 years (HR 2.3, 95% CI, 1.5–3.7, $P < 0.001$), >3 prior lines of therapy (HR 1.6, 95% CI, 1–2.6, $P = 0.03$) and high HCT-CI (HR 1.8, 95% CI, 1.1–2.9, $P = 0.02$) were independently associated with a lower PFS. Based on these four risk factors, we elaborated a risk model that differentiates three groups with different PFS probabilities (Fig. 1): 26% (95% CI, 9–43%; HR 4.8) with >2 risk factors, 41% (95% CI, 28–54%; HR 2.5) with 2 and 71% (95% CI, 60-82%; reference) with 0 or 1 risk factor ($P < 0.001$).

Donor type was not associated with any post-transplant outcomes (neutrophil engraftment, aGVHD, cGVHD, NRM, relapse/progression, PFS, OS, and GRFS), except for lower platelet engraftment in the haploidentical cohort (89% vs 98% in MSD and 98% in the MUD, $P < 0.001$).

This study shows that allo-HSCT in R/R FL offers an encouraging long-term PFS and a low relapse/progression incidence, supporting its potential for cure in this heavily pretreated cohort. Nevertheless, this benefit is counterbalanced by a high NRM. Regarding the comparison of donor types, there was no significant impact on survival outcomes.

The long-term PFS indicates that allo-HSCT offers survival with disease control in a high-risk population. Furthermore, age >50 years, non-CR status before allo-HSCT, > 3 prior lines of therapy, and high HCT-CI were associated with worse PFS, underlining the importance of patient's status and disease treatment on allo-HSCT outcomes. Of note, based on these four risk factors we were able to build a risk model that has important implications in determining transplant eligibility, especially in those with >1 risk factor who may benefit from non-transplant approaches.

However, the NRM rate was high. The primary causes of NRM were GHVD and infections, which did not vary significantly across the three different time periods, and are in line with most reports [1, 2, 5, 10]. Efforts to improve the prevention and management of these problems are clearly required. We show an independent negative effect of high HCT-CI on NRM, confirming its clinical utility to identify patients that may be benefiting from non-transplant treatments. We also identified other variables associated with higher NRM, such as age >50 years, >3 lines of therapy, and grade III–IV aGVHD. It is well-known that aGVHD leads to a high NRM in all lymphoma subtypes [11], while heavily pretreated patients and age have also been associated with higher mortality [1, 2].

The 9-year cumulative incidence of relapse/progression was very low. Later relapses may yet occur, but the plateau observed suggests that the use of allo-HSCT is curative in this high-risk group. This finding is, however, in contrast with some series [1, 2], where relapse ranged from 16 to 36%. Chemotherapy-resistant disease in our cohort is lower than the 15–25% reported [1–4, 12], which might have contributed to these results. However, the immune-mediated effect of graft-versus-lymphoma is probably the major contributing effect for long-term disease control, which is usually but not necessarily [12], associated with the development of GVHD. This effect is particularly exploited in the setting of RIC, which represented 88% of the conditioning regimens in our registry.

Table 1 Patient, disease, and transplant-related characteristics.

Characteristics	OveralL	MSD	MUD	Haploidentical	*P*
Patients, no. (%)	194 (100)	123 (64)	47 (24)	24 (12)	
Recipient age in years, median (range)	50 (29–70)	49 (29–67)	50 (31–70)	55 (39–70)	0.01
Male recipient, *n* (%)	126 (65)	80 (65)	31 (66)	15 (63)	0.9
Karnofsky score, *n* (%)					0.04
<80	9 (5)	6 (5)	1 (2)	2 (8)	
≥80	181 (93)	115 (93)	44 (94)	22 (92)	
Missing	4 (2)	2 (2)	2 (4)	0 (0)	
Ann-Arbor at diagnosis, *n* (%)					0.6
Stage 1–2	20 (10)	16 (13)	3 (6)	1 (4)	
Stage 3–4	171 (88)	104 (85)	44 (94)	23 (96)	
Missing	3 (2)	3 (2)	0 (0)	0 (0)	
Histology grade, *n* (%)					0.8
1	44 (23)	29 (24)	10 (21)	5 (21)	
2	54 (28)	33 (27)	10 (21)	11 (46)	
3a	43 (22)	29 (24)	8 (17)	6 (25)	
3b	14 (7)	9 (7)	4 (9)	1 (4)	
Missing	39 (20)	23 (18)	15 (32)	1 (4)	
FLIPI at diagnosis, *n* (%)					0.6
Low	25 (13)	17 (14)	4 (9)	4 (17)	
Intermediate	42 (21)	22 (18)	9 (19)	11 (46)	
High	44 (23)	26 (21)	11 (23)	7 (29)	
Missing	83 (43)	58 (47)	23 (49)	2 (8)	
Number of prior lines, *n* (%)					0.01
2	53 (28)	44 (36)	7 (15)	2 (8)	
3	58 (30)	34 (28)	15 (32)	9 (38)	
>3	80 (41)	43 (36)	24 (51)	13 (54)	
Missing	1 (1)	0 (0)	1 (2)	0 (0)	
Prior therapies, *n* (%)					
Anti-CD20	175 (90)	108 (88)	44 (94)	23 (96)	0.1
Anthracyclins	176 (91)	108 (88)	44 (94)	24 (100)	0.01
Platinum salts	116 (60)	69 (56)	32 (68)	15 (63)	0.2
Bendamustine	53 (27)	18 (15)	15 (32)	20 (83)	<0.001
PI3K inhibitor	8 (4)	0 (0)	3 (7)	5 (21)	<0.001
Prior autologous HSCT, *n* (%)	85 (44)	41 (33)	27 (57)	17 (71)	<0.001
PET before HSCT, *n* (%)	110 (57)	61 (50)	30 (64)	19 (79)	0.009
Years from diagnosis to allo-HSCT, median (range)	4 (1–21)	4 (1–21)	5 (1–15)	4 (1–12)	0.1
Remission status at HSCT, *n* (%)					0.8
CR	102 (52)	65 (53)	25 (53)	12 (50)	
PR	70 (36)	45 (37)	18 (38)	7 (29)	
NR or PD	19 (10)	11 (9)	3 (7)	5 (21)	
Missing	3 (2)	2 (1)	1 (2)	0 (0)	
HCT-CI, *n* (%)					0.9
Low	84 (43)	5 (41)	21 (45)	12 (50)	
Intermediate	57 (29)	37 (30)	14 (30)	6 (25)	
High	38 (20)	22 (18)	11 (23)	5 (21)	
Missing	15 (8)	13 (11)	1 (2)	1 (4)	

Table 1 (continued)

Characteristics	OveralL	MSD	MUD	Haploidentical	*P*
Disease risk index, *n* (%)					0.1
Low	172 (89)	110 (89)	43 (92)	19 (79)	
Intermediate	19 (10)	11 (9)	3 (6)	5 (21)	
Missing	3 (1)	2 (2)	1 (2)	0 (0)	
CMV serostatus, *n* (%)					<0.001
Donor + /recipient +	98 (51)	70 (57)	13 (27)	15 (63)	
Donor + /recipient−	20 (10)	14 (11)	4 (9)	2 (8)	
Donor−/recipient +	51 (26)	22 (18)	26 (55)	3 (12)	
Donor−/recipient−	17 (9)	9 (7)	4 (9)	4 (17)	
Missing	8 (4)	8 (7)	0 (0)	0 (0)	
Female donor to male recipient, *n* (%)	48 (25)	36 (29)	5 (11)	7 (29)	0.2
Intensity of conditioning regimen, *n* (%)					0.03
RIC	171 (88)	103 (84)	44 (94)	24 (100)	
MAC	23 (12)	20 (16)	3 (6)	0 (0)	
Conditioning regimen, *n* (%)					<0.001
Flu-Mel ± TBI	142 (73)	99 (80)	41 (88)	2 (8)	
Cy + TBI	9 (5)	8 (7)	1 (2)	0 (0)	
Flu-Bu-Cy	12 (6)	0 (0)	1 (2)	11 (46)	
TBF	7 (4)	2 (2)	2 (4)	3 (13)	
Others	24 (12)	14 (11)	2 (4)	8 (33)	
Campath, *n* (%)	13 (7)	9 (7)	4 (9)	0 (0)	0.3
Source of stem cells, *n* (%)					0.8
Bone marrow	19 (10)	12 (10)	4 (9)	3 (12)	
Peripheral blood	175 (90)	111 (90)	43 (91)	21 (88)	
GVHD prophylaxis, *n* (%)					<0.001
CNI + MTX + /− others	103 (53)	86 (70)	14 (30)	3 (12)	
CNI + MMF + /− others	44 (23)	28 (23)	11 (24)	5 (21)	
CNI + /− others	2 (1)	0	2 (4)	0 (0)	
Tac + Siro	23 (12)	8 (6)	15 (32)	0 (0)	
PT-Cy based	18 (9)	0	2 (4)	16 (67)	
Missing	4 (2)	1 (1)	3 (6)	0 (0)	
ATG, *n* (%)	25 (13)	12 (10)	13 (28)	0 (0)	0.01
Period of transplant, *n* (%)					<0.001
2000–2005	47 (24)	44 (36)	3 (6)	0 (0)	
2006–2011	82 (42)	58 (47)	23 (49)	1 (4)	
2012–2018	65 (34)	21 (17)	21 (45)	23 (96)	
Median follow-up, months (range)	108 (4–225)	125 (4–225)	98 (11–165)	39 (6–83)	<0.001

MSD matched sibling donor, *MUD* matched unrelated donor, *allo-HSCT* allogeneic hematopoietic stem cell transplantation, *CR* complete remission, *PR* partial remission, *NR* not remission, *PD* progression disease, *HCT-CI* hematopoietic cell transplantation-specific comorbidity index, *CMV* cytomegalovirus, *RIC* reduced-intensity conditioning, *MAC* myeloablative conditioning, *Flu* fludarabine, *Mel* melphalan, *TBI* total body irradiation, *Cy* cyclophosphamide, *TBF* thiotepa-busulfan-fludarabine, *CNI* calcineurin inhibitor, *MTX* methotrexate, *MMF* mycophenolate mofetil, *Tac* tacrolimus, *Siro* sirolimus, *PT-Cy* post-transplant cyclophosphamide, *ATG* anti-thymocyte globulin.

We report for the first-time equivalent outcomes across three donor types regarding GVHD, relapse, NRM, and PFS in a real-life clinical setting. Our findings suggest that in the absence of the HLA-identical sibling donor, allo-HSCT should not be delayed by searching for an unrelated donor. The most rapidly available donor should be chosen, which in most cases is a haploidentical donor. In this sense, it should be considered to refer patients to allo-HSCT before the 4th treatment line, as the NRM increases significantly when patients are transplanted after the 3rd line of therapy.

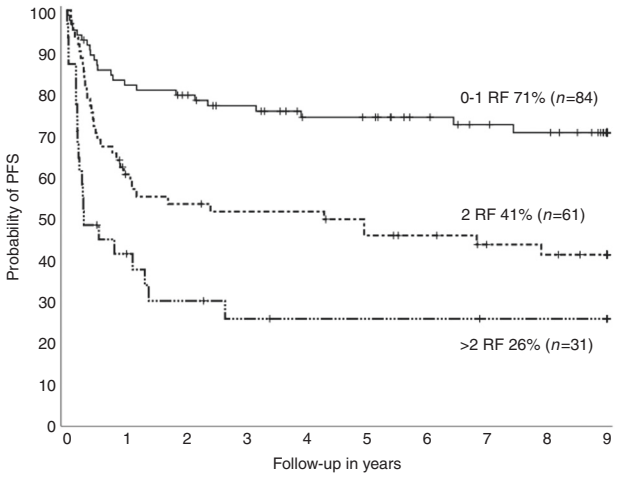

Fig. 1 PFS according to the number of independent risk factors (RF). Age >50 years, non-CR status before allo-HSCT, >3 prior lines of therapy and high HCT-CI were the variables associated with worse PFS.

We acknowledge that our study has several limitations, with the retrospective design being the foremost. Lymphoma treatments, conditioning regimens, and GVHD prophylaxis within donor groups were heterogeneous and included a small number of patients in the haploidentical cohort. Also, the frequency of Karnofsky PS < 80 was low in our study and we were unable to demonstrate any association between Karnofsky score and its impact on NRM or PFS/OS.

In summary, allo-HSCT confers high response rates and prolongs PFS in R/R FL patients regardless of donor type, especially in recipients <50 years with low HCT-CI, while their disease remains chemoresponsive and before the failure of multiple lines of chemotherapy. Additional studies using a uniform GVHD prophylaxis would be important to confirm the equivalence on transplant outcomes comparing donors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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