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Influence of donor type, stem cell source and conditioning on outcomes after haploidentical transplant for lymphoma – a LWP-EBMT study

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Summary

Haploidentical stem cell transplantation (haploSCT) is becoming a major transplant modality for lymphoma. To assess the effects of donor characteristics, stem cell source and conditioning on outcomes, we identified 474 adults with Hodgkin (HL; 240), peripheral T-cell (PTCL; 88), diffuse large B-cell (77), mantle cell (40) or follicular lymphoma (FL; 29), who received haploSCT with post-transplant cyclophosphamide. Median follow-up of alive patients was 32 months. On multivariate analysis, acute graft-versus-host disease (GVHD) grade 2–4 was lower with offspring donors or bone marrow cells, whereas extensive chronic GVHD was higher in partial response at haploSCT or when using sisters, haploidentical donors beyond first degree, or female donors in male patients. Progression-free survival (PFS) was better for FL, HL and PTCL, whereas overall survival (OS) was better for HL and PTCL. Complete remission at haploSCT improved PFS and OS whereas these were negatively affected by cytomegalovirus donor positive/recipient positive status. No other donor characteristics (age, gender, human leucocyte antigen mismatch, ABO incompatibility) affected PFS or OS except use of haploidentical donors beyond first degree, which negatively affected OS. PFS and OS are mostly influenced by disease status and lymphoma subtype, supporting the use of any first degree haploidentical family member as a donor.

Keywords: donor type, stem cell source, conditioning, haploidentical transplant, lymphoma.

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Despite the increasing use of targeted therapies, allogeneic stem cell transplantation (SCT) remains an important and potentially curative treatment modality for patients with lymphoma, particularly for those who progress after autologous SCT. For patients with no human leucocyte antigen (HLA) identical donor, a haploidentical transplant (haploSCT) is becoming a major alternative. HaploSCT was historically performed using T-cell depleted grafts (Aversa *et al*, 1998) or T-cell replete grafts after intense immunosuppression (Wang *et al*, 2013). However, because of its wide applicability and an increased body of evidence of its efficacy and safety (Luznik *et al*, 2008; Bashey *et al*, 2013; Ciurea *et al*, 2015; McCurdy *et al*, 2015; Dietrich *et al*, 2016; Kanate *et al*, 2016; Hamadani *et al*, 2018), T-cell replete grafts with post-transplant cyclophosphamide (ptCy) has become the principal modality of haploSCT for patients with haematological malignancies, including lymphoma.

HaploSCT with ptCy was initially developed by the Baltimore group using a nonmyeloablative (NMA) conditioning regimen with fludarabine, cyclophosphamide (FC), low dose total body irradiation (TBI) and unmanipulated bone marrow (BM) (Luznik *et al*, 2008). The same group described an algorithm for donor selection based on donor age, gender and cytomegalovirus (CMV) serostatus as well as donor-recipient ABO compatibility, and donor-specific antibodies (DSA) in the patient (Kasamon *et al*, 2010). Other algorithms incorporating non-inherited maternal antigen mismatch were reported for T-cell depleted haploSCT recommending maternal donors as first choice (Stern *et al*, 2008), whereas for the Asian protocol of T-cell replete haploSCT with intense immunosuppression, offspring donors were recommended as the first choice (Wang *et al*, 2014). A recent study from the Center for International Blood and Marrow Transplant Research (CIBMTR) of 928 haploSCTs with ptCy in patients with haematological malignancies (predominantly acute leukaemia), reported that the effect of donor age on survival is counteracted by the effect of patient age, and that survival did not differ between sibling and offspring donor transplantation (McCurdy *et al*, 2018).

Overall, there is little data on how to select the best haploidentical donor when multiple potential donors are available, as well as the ideal stem cell source and conditioning regimen in the setting of haploSCT with ptCy for lymphoma. The purpose of this study was to address these questions using a large sample from the European Society for Blood and Marrow Transplantation (EBMT) registry.

Methods

Study design and data collection

This is a retrospective registry-based, multicentre analysis. Data were provided and approved for this study by the Lymphoma Working Party (LWP) of the EBMT. The EBMT is a voluntary working group of more than 600 transplant centres, which are required annually to report all consecutive SCTs and follow-up. Audits are routinely performed to determine the accuracy of the data. Since 1 January 2003, all transplant centres have been required to obtain written informed consent prior to data registration with the EBMT, following the Helsinki Declaration of 1975. Eligibility criteria for this analysis included adult patients (age >18 years) with Hodgkin lymphoma (HL), peripheral T cell lymphoma (PTCL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) or follicular lymphoma (FL), who had received a haploSCT with ptCy between 2010 and 2016 at EBMT participating centres. The stem cell source included BM or peripheral blood stem cells (PBSC).

Variables collected included recipient and donor age and gender, previous pregnancies for female donors, date of diagnosis, lymphoma subtype, prior autologous SCT, disease and positron emission tomography-computed tomography scan status at haploSCT, Karnofsky score at the time of transplant, transplant-related factors, including year of transplant, conditioning regimen, *in vivo* T-cell depletion, graft-versus-host disease (GVHD) prophylaxis, stem cell source, donor relationship to recipient (father, mother, brother, sister, son, daughter, other family member), patient and donor ABO compatibility and HLA mismatch, and patient and donor CMV serological status. As many of these variables are not routinely collected in the EBMT registry, a specific questionnaire was sent to participating centres.

Definitions

The histological diagnosis was based on local review, and patients were staged according to the Ann Arbor system. Disease status at transplantation was classified as complete remission (CR), partial response (PR) or refractory disease. Disease status was assessed by the local team according to the Revised Response Criteria for Malignant Lymphoma (Cheson *et al*, 2007) and to the institutional standard of care.

Myeloablative conditioning (MAC) was defined as a regimen containing either total body irradiation (TBI) with a dose greater than 6 Gy, a total dose of oral busulfan greater than 8 mg/kg, or a total dose of intravenous busulfan greater than 6·4 mg/kg. All other regimens were defined as reduced intensity conditioning (RIC) (Bacigalupo *et al*, 2009). The diagnosis and grading of acute GVHD (aGVHD; Glucksberg *et al*, 1974) and chronic GVHD (cGVHD; Terwey *et al*, 2012) was performed by transplant centres using the standard criteria.

Statistical analysis

Endpoints included progression-free survival (PFS), overall survival (OS) non-relapse mortality (NRM), relapse incidence (RI), aGVHD and cGVHD. All outcomes were measured from the time of haploSCT. PFS was defined as survival without lymphoma relapse or progression; patients alive without lymphoma relapse or progression were censored at the time of last contact. OS was defined as death from any cause. NRM was defined as death without previous lymphoma relapse. The probabilities of OS and PFS were calculated by using the Kaplan-Meier method. Cumulative incidence functions were used to estimate RI and NRM in a competing risk setting. Death and relapse were considered as competing events for acute and chronic GVHD. For univariate analyses, continuous variables were categorized and the median used as a cut-off point. Univariate comparisons were performed using the log-rank test for PFS and OS and Gray's test for cumulative incidences. A Cox proportional hazards model was used for multivariate regression. Variables included in the multivariate analysis were lymphoma subtype, disease status at transplant (CR, PR, refractory disease), patient age (by 5-year increments), donor to patient gender, relationship of the donor to the recipient (parent, sibling or offspring for acute GVHD; mother, father, sister, brother, daughter, son, other family member for the other outcomes), ABO incompatibility (isogroup, minor, major and bidirectional incompatibility), CMV donor/recipient status (negative/negative, negative/positive, positive/negative, positive/positive), conditioning (MAC or RIC), and stem cell source (BM or PBSC).

Results are expressed as a hazard ratio (HR) with 95% confidence intervals (CI). All tests were two sided. The type-1 error rate was fixed at 0·05 for determination of factors associated with time to event outcomes. All analyses were performed using SPSS 24.0 (SPSS Inc, Chicago, IL, USA) and R version 3.4.0 (R Core Team, 2014).

Results

Patients, donors and transplant characteristics

Patients, donors and transplant characteristics are summarized in Tables I and II. Forty-six percent of donors were female, including 105 (25%) with prior pregnancies. Median follow-up of alive patients was 32 months (range 3–93).

Engraftment and graft-versus-host disease

Neutrophil engraftment by day 100 was successful in 95% of patients. Multivariable Cox analysis showed that the use of PBSC had a positive impact on engraftment (Table III).

The cumulative incidence of aGVHD grade II–IV and grade III–IV at day 100 was 32% and 8% of patients respectively, and was significantly increased when PBSCs were used. Results of the multivariate analysis are shown in Table IV. The 2-year cumulative incidence of cGVHD and extensive cGVHD was 25% and 9%, respectively. Multivariate analysis is shown in Table V.

Relapse and non-relapse mortality

The 2-year RI and NRM were 29% and 19%, respectively (Fig 1A, 1). Table V shows the results of multivariable analysis for RI and NRM.

Table I. Patients characteristics.

Characteristic	*N* (%)
Number of patients	474 (100)
Age (years) at haploSCT; median (range)	41 (18–72)
Female	164 (35)
Cytomegalovirus serology positive	305 (65)
Lymphoma subtype	
Diffuse large B-cell lymphoma	77 (16)
Follicular lymphoma	29 (6)
Hodgkin lymphoma	240 (51)
Mantle cell lymphoma	40 (8)
Peripheral T-cell lymphoma	88 (19)
Prior autologous stem cell transplantation	329 (69)
Disease status at haploSCT [missing]	[3]
CR	228 (48)
PR	156 (33)
Refractory disease	87 (19)
PET status at haploSCT [missing]	[9]
Negative	212 (46)
Positive	211 (45)
Not evaluated	42 (9)

CR, complete response; haploSCT, haplo-identical stem cell transplantation; PET, positron emission tomography; PR, partial response. Bold values are statistically significant (P<0.05).

Table II. Donor and transplant characteristics.

Donor and transplant characteristics	*N* (%)
Age of the donor, years; median (range)	42 (13–85)
ABO compatibility	
Isogroup	303 (64)
Bidirectional incompatibility	16 (3)
Major incompatibility	77 (16)
Minor incompatibility	78 (17)
Cytomegalovirus status	
D−/R−	94 (20)
D−/R+	66 (14)
D+/R−	69 (15)
R+/R+	237 (51)
Female	215 (46)
Relationship to recipient [missing]	[4]
Brother	131 (28)
Daughter	52 (11)
Father	52 (11)
Mother	68 (15)
Other family member	15 (3)
Sister	86 (18)
Son	66 (14)
HLA mismatch [missing]	[46]
3/6	308 (72)
4/6	106 (25)
5/6	14 (3)
Year of haploSCT	2014 (2010–2016)
Conditioning intensity [missing]	[2]
RIC	365 (77)
MAC	107 (23)
Donor to patient sex [missing]	[1]
Female to female	81 (17)
Female to male	134 (28)
Male to female	82 (17)
Male to male	176 (37)
Stem cell source PBSC	255 (54)

D, donor; haploSCT, haplo-identical stem cell transplantation; HLA, human leucocyte antigen; MAC, myeloablative conditioning regimen; PBSC, peripheral blood stem cells; R, recipient; RIC, reduced intensity conditioning regimen.

Progression-free and overall survival

The 2-year PFS and OS were 57% and 72% respectively for HL; 54% and 62% for PTCL; 35% and 35% for DLBCL; 52% and 61% for MCL and 56% and 56% for FL (Fig 2A, 2). The results of multivariate analysis for PFS and OS are shown in Table V.

Discussion

Here we report the largest study on the influence of donor characteristics, stem cell source and conditioning in haploSCT with ptCy for lymphoma. Whereas availability of an HLA-identical donor represents an important limitation for matched sibling or matched unrelated SCT, multiple haploidentical donors are often available and the identification of the best donor, with little available data to rely on, becomes a dilemma. Maternal donors were recommended as first choice in the setting of T-cell depleted haploSCT (Stern *et al*, 2008). Conversely, offspring donors taking into consideration the non-inherited maternal antigen mismatch were recommended as first choice for the Asian protocols of T-cell replete haploSCT with intense immunosuppression (Wang *et al*, 2014). In the setting of haploSCT with ptCy, using a large dataset of haematological malignancies (predominantly acute leukaemia), the CIBMTR recently reported that the effect of donor age on survival is counteracted by the effect of patient age, and that survival does not differ between sibling and offspring donor transplantation (McCurdy *et al*, 2018).

In our study, we did not find any influence of donor age on transplant outcomes. However, we found that, compared to haploidentical sibling donors, the use of offspring donors decreased the risk of aGVHD grade II-IV, in agreement with the Asian results (Wang *et al*, 2014). Importantly, and contrary to the CIBMTR study, we showed that the use of female donors in male patients significantly increased the risk of cGVHD and extensive cGVHD, without affecting other transplant outcomes. Similarly, the use of sisters or haploidentical donors beyond first degree, regardless of the patient gender, significantly increased the risk of extensive cGVHD, with decreased OS when using haploidentical donors beyond first degree. This negative effect of female haploidentical donors in male patients, or haploidentical

Table III. Multivariate analysis for engraftment.

	HR (95% CI) P
Diagnosis (ref = DLBCL)	
Follicular lymphoma	1·42 (0·89–2·25) $P = 0{\cdot}14$
Hodgkin lymphoma	1·22 (0·9–1·67) $P = 0{\cdot}20$
Mantle cell lymphoma	1·5 (0·97–2·31) $P = 0{\cdot}07$
Peripheral T-cell lymphoma	1·08 (0·77–1·51) $P = 0{\cdot}66$
Disease status at SCT (ref = CR)	
Partial response	0·91 (0·73–1·14) $P = 0{\cdot}421$
Primary refractory, progression, relapse	0·77 (0·58–1·01) $P = 0{\cdot}06$
Patient age at SCT (5-year increments)	0·97 (0·92–1·02) $P = 0{\cdot}23$
Donor to patient sex (ref = female to female)	
Female to male	0·91 (0·67–1·24) $P = 0{\cdot}553$
Male to female	2·94 (0·91–9·49) $P = 0{\cdot}07$
Male to male	3·07 (0·98–9·65) $P = 0{\cdot}06$
Relationship to recipient (ref = brother)	
Daughter	2·59 (0·79–8·5) $P = 0{\cdot}12$
Father	0·82 (0·56–1·19) $P = 0{\cdot}29$
Mother	2·7 (0·81–8·95) $P = 0{\cdot}105$
Other family member	2·27 (0·93–5·54) $P = 0{\cdot}07$
Sister	2·84 (0·88–9·21) $P = 0{\cdot}08$
Son	0·81 (0·57–1·14) $P = 0{\cdot}23$
ABO incompatibility (ref = isogroup)	
Bidirectionnal incompatibility	1·5 (0·84–2·66) $P = 0{\cdot}17$
Major incompatibility	0·99 (0·75–1·3) $P = 0{\cdot}95$
Minor incompatibility	1·06 (0·81–1·4) $P = 0{\cdot}66$
CMV donor to patient (ref = neg to neg)	
Donor negative recipient positive	0·76 (0·54–1·08) $P = 0{\cdot}12$
Donor positive recipient negative	0·89 (0·64–1·25) $P = 0{\cdot}52$
Donor positive recipient positive	0·79 (0·61–1·03) $P = 0{\cdot}08$
Conditioning regimen, MAC *versus* RIC	1·1 (0·85–1·43) 1·2 $P = 0{\cdot}46$
Stem cell source PBSC *versus* BM	**1·52 (1·24–1·87)** $\mathbf{P < 0{\cdot}001}$

BM, bone marrow; CI, confidence interval; CMV, cytomegalovirus; CR, complete response; DLBCL, diffuse large cell lymphoma; HR, hazard ratio, MAC, myeloablative conditioning; neg, negative; PBSC, peripheral blood stem cells; ref, reference; RIC, reduced intensity conditioning; SCT, stem cell transplantation. Bold values are statistically significant (P<0.05).

sisters or donors beyond first degree, independently from the patient gender, has not been previously reported in the setting of haploSCT with ptCy, and can have direct practical implications on donor selection, particularly if confirmed in future studies.

We also found that the donor and recipient CMV status affected transplant outcomes including PFS and OS. Several previous reports have demonstrated that donor and/or recipient CMV seropositivity results in an OS decline in patients with chronic haematological malignancies who have undergone allogeneic SCT (alloSCT) (Schmidt-Hieber *et al*, 2019). In agreement with these results, we found that the combination of CMV recipient positive-donor positive was associated with decreased PFS and OS. However, it is unclear why only the combination of CMV recipient positive-donor negative resulted in increased risk of aGVHD in the setting of haploSCT for lymphoma. In contrast, other donor characteristics, such as prior donor pregnancy, ABO incompatibility, and degree of HLA mismatch had no impact, except for an unexpected increased incidence of relapse for bidirectional ABO incompatibility. Contradictory results have been previously reported regarding the effect of ABO incompatibility in the setting of haploSCT: whereas an EBMT study showed that bidirectional ABO mismatch increased the risk of aGVHD (Canaani *et al*, 2017), no impact of ABO mismatch was reported in the CIBMTR study (McCurdy *et al*, 2018). Nevertheless, we acknowledge the limitations of our study regarding the impact of HLA-related factors. Indeed, the relatively small sample size to assess HLA influence, the lack of availability of parental HLA for sibling haplo-identical donors to assess the effect of the non-inherited maternal antigen mismatch, and the lack of data on donor specific antibodies and desensitization protocols, preclude a direct assessment of the impact of HLA-related factors on transplant outcomes in our study.

Another frequent dilemma when performing haploSCT for lymphoma is the choice of the best conditioning regimen and the best source of stem cells. Our results indicate that PFS and OS were not affected by the conditioning and, therefore, there is no advantage in using more intense conditioning regimens for lymphoma. Finally, although PBSC improved engraftment, it increased the risk of aGVHD. Overall, both sources of stem cells produced similar results in term of PFS and OS.

Table IV. Multivariate analysis for acute graft-versus-host disease.

	Acute GVHD Grade II–IV HR (95% CI) *P*	Acute GVHD Grade III–IV HR (95% CI) *P*
Diagnosis (ref = DLBCL)		
Follicular lymphoma	1·98 (0·97–4·03) *P* = 0·06	2·13 (0·33–13·57) *P* = 0·42
Hodgkin lymphoma	0·9 (0·52–1·54) *P* = 0·70	2·62 (0·71–9·71) *P* = 0·15
Mantle cell lymphoma	1·23 (0·62–2·46) *P* = 0·55	2·49 (0·5–12·32) *P* = 0·26
Peripheral T-cell lymphoma	0·89 (0·49–1·6) *P* = 0·69	2·39 (0·62–9·24) *P* = 0·21
Disease status at SCT (ref = CR)		
Partial response	0·86 (0·59–1·25) *P* = 0·43	0·68 (0·3–1·53) *P* = 0·35
Primary refractory progression, relapse	0·71 (0·41–1·21) *P* = 0·21	1·6 (0·65–3·91) *P* = 0·31
Patient age at SCT (5-year increments)	1·07 (0·98–1·17) *P* = 0·15	1·15 (0·95–1·39) *P* = 0·14
Donor to patient sex (ref = female to female)		
Female to male	0·77 (0·44–1·37) *P* = 0·38	0·95 (0·3–3·04) *P* = 0·93
Male to female	0·88 (0·47–1·63) *P* = 0·69	0·87 (0·24–3·17) *P* = 0·83
Male to male	1·03 (0·62–1·72) *P* = 0·91	1·04 (0·36–2·99) *P* = 0·95
Relationship to recipient (ref = brother/sister)		
Father/Mother	0·99 (0·61–1·59) *P* = 0·96	1·42 (0·54–3·73) *P* = 0·48
Son/Daughter	**0·54 (0·33–0·89) *P* = 0·015**	0·61 (0·23–1·61) *P* = 0·32
ABO incompatibility (ref = isogroup)		
Bidirectional incompatibility	0·6 (0·19–1·94) *P* = 0·40	0·7 (0·09–5·57) *P* = 0·73
Major incompatibility	0·9 (0·55–1·46) *P* = 0·66	0·44 (0·13–1·47) *P* = 0·18
Minor incompatibility	1·23 (0·77–1·95) *P* = 0·39	0·44 (0·13–1·48) *P* = 0·19
CMV donor to patient (ref = neg to neg)		
Donor negative recipient positive	1·15 (0·66–2·02) *P* = 0·62	**5·07 (1–25·73) *P* = 0·05**
Donor positive recipient negative	0·91 (0·51–1·64) *P* = 0·76	3·34 (0·62–18·11) *P* = 0·16
Donor positive recipient positive	0·78 (0·49–1·23) *P* = 0·28	4·04 (0·92–17·75) *P* = 0·07
Conditioning regimen (MAC *versus* RIC)	1·01 (0.66–1.55) 1·02 *P* = 0·95	1 (0·43–2·32) *P* = 0·99
Stem cell source PBSC *versus* BM	**2·15 (1·48–3·12) *P* < 0·001**	**4·57 (1·85–11·28) *P* < 0·001**

BM, bone marrow; CI, confidence interval; CMV, cytomegalovirus; CR, complete response; DLBCL, diffuse large cell lymphoma; GVHD, graft-versus-host disease; HR, hazard ratio, MAC, myeloablative conditioning; neg, negative; PBSC, peripheral blood stem cells; ref, reference; RIC, reduced intensity conditioning; SCT, stem cell transplantation. Bold values are statistically significant (P<0.05).

Another important finding of our study is the encouraging results for 2-year PFS and OS, exceeding 50% for HL, PTCL, FL and MCL. The results were particularly good for patients transplanted in CR, emphasizing the need to achieve CR prior to transplant, whenever possible. With the limitation of potential selection bias, these results strongly suggest that

Table V. Multivariate analysis for overall survival, progression-free survival, incidence of relapse, non-relapse mortality, chronic graft-versus-host disease (cGVHD), extensive cGVHD.

	OS HR (95% CI) *P*	PFS HR (95% CI) *P*	IR HR (95% CI) *P*	NRM HR (95% CI) *P*	cGVHD HR (95% CI) *P*	Extensive cGVHD HR (95% CI) *P*
Diagnosis (ref = DLBCL)						
Follicular lymphoma	0·52 (0·26–1·04)	**0·47 (0·23–0·93)**	**0·33 (0·11–0·97)**	0·6 (0·24–1·48)	0·81 (0·24–2·76)	0·74 (0·06–8·61)
	P = 0·06	***P* = 0·03**	***P* = 0·04**	*P* = 0·27	*P* = 0·74	*P* = 0·81
Hodgkin lymphoma	**0·48 (0·31–0·73)**	**0·5 (0·34–0·75)**	**0·48 (0·28–0·82)**	0·56 (0·31–1·03)	1·14 (0·54–2·43)	1·64 (0·41–6·61)
	***P* < 0·001**	***P* < 0·001**	***P* = 0·007**	*P* = 0·06	*P* = 0·73	*P* = 0·48
Mantle cell lymphoma	0·54 (0·29–1·01)	0·58 (0·32–1·03)	0·71 (0·31–1·59)	0·46 (0·2–1·08)	1 (0·36–2·77)	0·59 (0·08–4·39)
	P = 0·052	*P* = 0·065	*P* = 0·40	*P* = 0·08	*P* = 0·99	*P* = 0·60
Peripheral T-cell lymphoma	**0·53 (0·34–0·84)**	**0·59 (0·38–0·91)**	0·73 (0·41–1·29)	**0·43 (0·21–0·86)**	1·19 (0·53–2·67)	0·75 (0·15–3·75)
	***P* = 0·006**	***P* = 0·017**	*P* = 0·28	***P* = 0·018**	*P* = 0·68	*P* = 0·73
Disease status at SCT (ref = CR)						
Partial response	**1·56 (1·09–2·23)**	**1·81 (1·31–2·5)**	**2·2 (1·43–3·4)**	1·35 (0·82–2·23)	**1·84 (1·14–2·96)**	**2·53 (1·08–5·89)**
	***P* = 0·015**	***P* < 0·001**	***P* < 0·001**	*P* = 0·236	***P* = 0·012**	***P* = 0·032**
Primary refractory, progression, relapse	**3·04 (2·08–4·43)**	**3·43 (2·41–4·87)**	**4·54 (2·86–7·18)**	**2·58 (1·47–4·52)**	1·39 (0·72–2·67)	2·24 (0·73–6·89)
	***P* < 0·001**	***P* < 0·001**	***P* < 0·001**	***P* < 0·001**	*P* = 0·33	*P* = 0·16
Patient age at SCT (5-year increments)	1·03 (0·95–1·12)	1 (0·93–1·08)	0·92 (0·83–1·01)	**1·15 (1·02–1·29)**	0·99 (0·89–1·11)	1·15 (0·95–1·38)
	P = 0·43	*P* = 0·91	*P* = 0·09	***P* = 0·025**	*P* = 0·91	*P* = 0·15
Donor to patient sex (ref = female to female)						
Female to male	0·78 (0·48–1·27)	1·09 (0·69–1·7)	1·33 (0·72–2·46)	0·82 (0·42–1·61)	**2·51 (1·28–4·95)**	**3·64 (1·09–12·09)**
	P = 0·32	*P* = 0·72	*P* = 0·36	*P* = 0·57	***P* = 0·008**	***P* = 0·035**
Male to female	1·77 (0·41–7·69)	2·2 (0·51–9·54)	4·51 (0·65–31·13)	0·7 (0·05–9·42)	2·97 (0·3–29·1)	9·47 (0·28–318·79)
	P = 0·45	*P* = 0·29	*P* = 0·126	*P* = 0·786	*P* = 0·35	*P* = 0·21
Male to male	1·88 (0·44–7·93)	2·32 (0·55–9·83)	4·75 (0·71–31·75)	0·75 (0·06–9·78)	3·63 (0·41–32·22)	19·92 (0·72–551·69)
	P = 0·39	*P* = 0·25	*P* = 0·11	*P* = 0·83	*P* = 0·25	*P* = 0·08
Relationship to recipient (ref = brother)						
Daughter	1·61 (0·35–7·33)	2·1 (0·47–9·41)	4·14 (0·58–29·83)	0·69 (0·05–9·81)	2·07 (0·22–19·69)	9·95 (0·26–380·23)
	P = 0·54	*P* = 0·33	*P* = 0·16	*P* = 0·79	*P* = 0·53	*P* = 0·22
Father	1·18 (0·64–2·16)	1·51 (0·89–2·55)	1·81 (0·96–3·41)	0·93 (0·32–2·66)	0·67 (0·28–1·59)	2·03 (0·41–10·13)
	P = 0·60	*P* = 0·13	*P* = 0·07	*P* = 0·89	*P* = 0·36	*P* = 0·39
Mother	2·68 (0·6–11·97)	2·94 (0·66–12·96)	4·79 (0·68–33·73)	1·35 (0·1–18·4)	1·37 (0·14–13·47)	10·91 (0·33–364·08)
	P = 0·20	*P* = 0·16	*P* = 0·12	*P* = 0·82	*P* = 0·79	*P* = 0·18
Other family member	**2·71 (1–7·34)**	2·26 (0·84–6·08)	2·39 (0·75–7·61)	1·77 (0·22–14·44)	3·34 (0·66–16·96)	**31·95 (2·43–420·33)**
	***P* = 0·05**	*P* = 0·11	*P* = 0·14	*P* = 0·59	*P* = 0·15	***P* = 0·008**
Sister	2·57 (0·6–11·08)	2·68 (0·62–11·48)	4·84 (0·72–32·68)	0·98 (0·07–12·99)	3·66 (0·41–32·35)	**34·44 (1·24–960·34)**
	P = 0·20	*P* = 0·19	*P* = 0·11	*P* = 0·99	*P* = 0·24	***P* = 0·037**
Son	1·3 (0·79–2·14)	1·43 (0·9–2·29)	1·56 (0·81–3·02)	1·23 (0·63–2·42)	0·54 (0·22–1·34)	0·39 (0·04–3·46)
	P = 0·30	*P* = 0·13	*P* = 0·19	*P* = 0·54	*P* = 0·19	*P* = 0·40
ABO incompatibility (ref = isogroup)						

Table V. (*Continued*)

	OS HR (95% CI) *P*	PFS HR (95% CI) *P*	IR HR (95% CI) *P*	NRM HR (95% CI) *P*	cGVHD HR (95% CI) *P*	Extensive cGVHD HR (95% CI) *P*
Bidirectionnal incompatibility	1·34 (0·68–2·63) *P* = 0·39	1·48 (0·77–2·84) *P* = 0·24	**2·83 (1·35–5·9)** ***P* = 0·006**	0·23 (0·03–1·74) *P* = 0·15	0·7 (0·15–3·25) *P* = 0·65	0·72 (0·08–6·84) *P* = 0·78
Major incompatibility	0·81 (0·51–1·27) *P* = 0·36	0·93 (0·63–1·39) *P* = 0·73	1·04 (0·62–1·74) *P* = 0·88	0·8 (0·42–1·52) *P* = 0·50	0·85 (0·46–1·57) *P* = 0·61	0·64 (0·2–2·02) *P* = 0·45
Minor incompatibility	0·92 (0·6–1·43) *P* = 0·72	0·95 (0·63–1·41) *P* = 0·78	0·84 (0·48–1·46) *P* = 0·53	1·1 (0·61–1·97) *P* = 0·76	1·53 (0·89–2·62) *P* = 0·12	0·65 (0·2–2·09) *P* = 0·47
CMV donor to patient (ref = neg to neg)						
Donor negative recipient positive	1·51 (0·89–2·56) *P* = 0·13	1·58 (0·97–2·57) *P* = 0·07	1·53 (0·82–2·86) *P* = 0·18		1·02 (0·46–2·23) *P* = 0·97	1·6 (0·25–10·17) *P* = 0·62
Donor positive recipient negative	0·69 (0·36–1·33) *P* = 0·26	1·03 (0·6–1·75) *P* = 0·92	1·02 (0·53–1·96) *P* = 0·95		0·98 (0·47–2·05) *P* = 0·96	1·39 (0·29–6·55) *P* = 0·68
Donor positive recipient positive	**1·61 (1·05–2·47)** ***P* = 0·029**	**1·56 (1·05–2·33)** ***P* = 0·027**	1·34 (0·81–2·22) *P* = 0·25		1·26 (0·71–2·22) *P* = 0·44	2·63 (0·73–9·49) *P* = 0·14
Conditioning regimen, MAC *versus* RIC	1·04 (0·71–1·51) *P* = 0·84	0·88 (0·62–1·26) *P* = 0·50	0·97 (0·61–1·54) *P* = 0·89		0·73 (0·4–1·34) *P* = 0·32	0·47 (0·14–1·65) *P* = 0·24
Stem cell source PBSC *versus* BM	1·32 (0·97–1·8) *P* = 0·08	0·97 (0·73–1·28) *P* = 0·83	0·84 (0·58–1·2) *P* = 0·34		0·83 (0·53–1·28) *P* = 0·39	1·86 (0·8–4·33) *P* = 0·15

BM, bone marrow; cGVHD, chronic graft-versus-host disease; CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio, IR, incidence of relapse; MAC, myeloablative conditioning; neg, negative; NRM, non-relapse mortality; OS, overall survival; PBSC, peripheral blood stem cells; PFS, progression-free survival; ref, reference; RIC, reduced intensity conditioning; SCT, stem cell transplantation. Bold values are statistically significant ($P<0.05$).

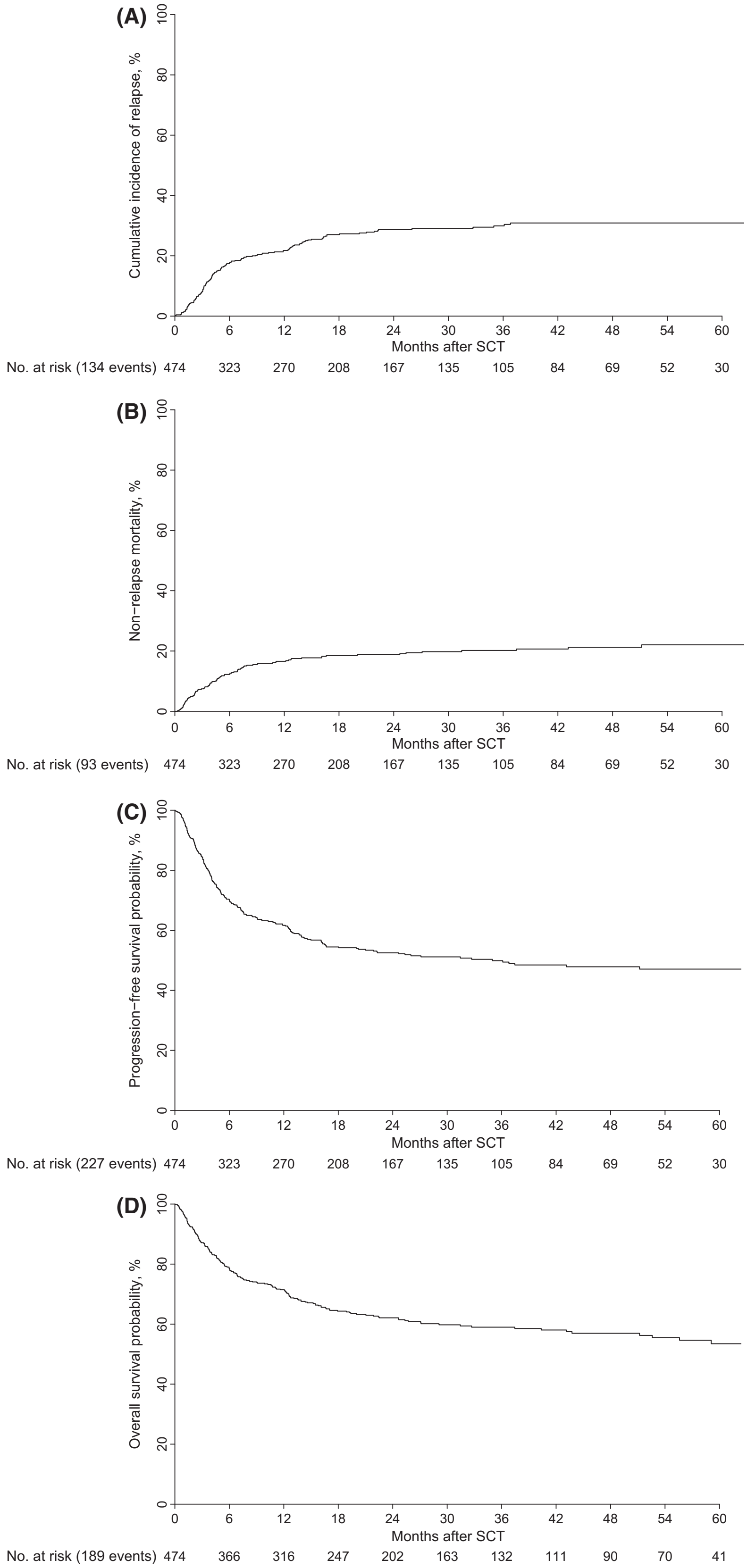
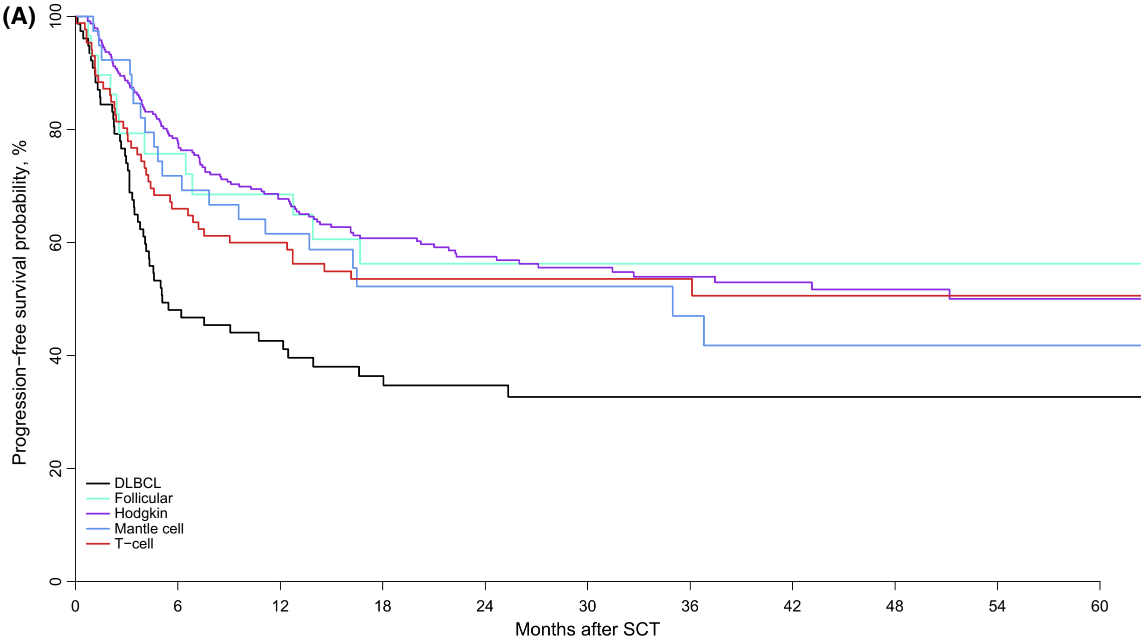
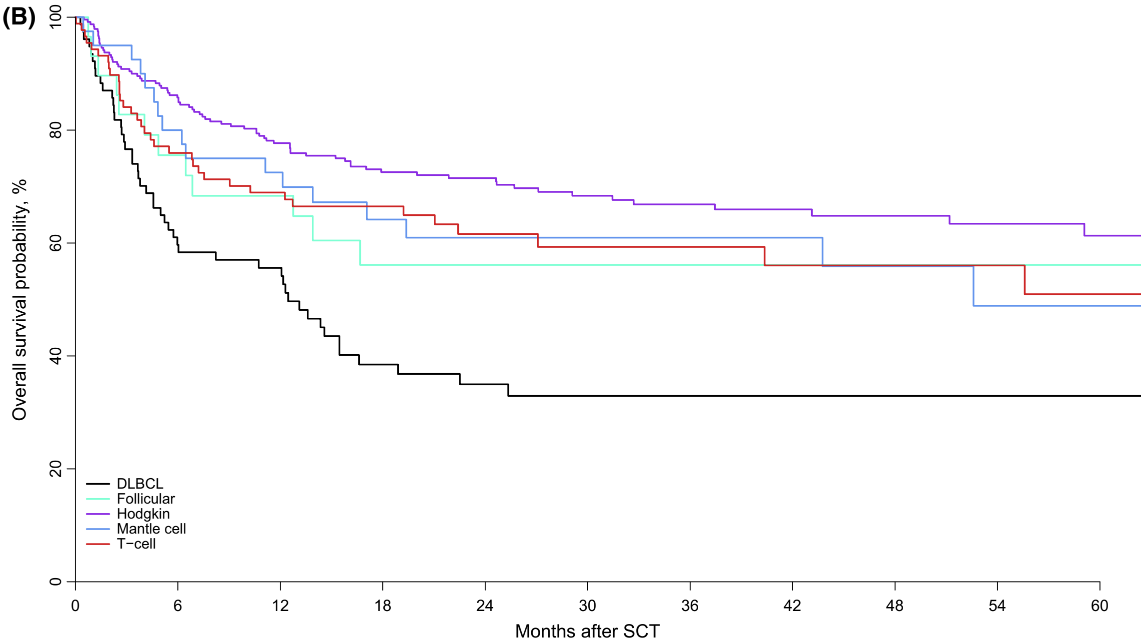


Fig 1. Transplant outcomes. (A) Incidence of relapse; (B) Non-relapse mortality; (C) Progression-free survival; (D) Overall survival. SCT, stem cell transplantation.



No. at risk											
DLBCL (50 events)	77	41	48	55	59	61	66	68	70	70	73
Follicular (12 events)	29	8	10	16	17	18	18	18	21	25	26
Hodgkin (105 events)	240	55	87	118	142	162	182	194	202	211	222
Mantle cell (20 events)	40	11	16	23	27	28	30	32	34	34	37
T-cell (40 events)	88	31	38	49	57	65	68	73	73	77	81



No. at risk											
DLBCL (48 events)	77	32	39	54	59	61	66	68	70	70	73
Follicular (12 events)	29	8	10	16	17	18	18	18	21	25	26
Hodgkin (77 events)	240	37	65	94	116	142	164	177	189	199	215
Mantle cell (17 events)	40	8	12	19	24	25	26	27	31	33	36
T-cell (35 events)	88	23	32	44	56	65	68	73	73	77	83

Fig 2. Transplant outcomes by lymphoma subtype. (A) Progression-free survival; (B) Overall survival. DLBCL, diffuse large B-cell lymphoma; SCT, stem cell transplantation; T-cell, peripheral T-cell lymphoma.

haploSCT with ptCy is an efficacious treatment modality for relapsed/refractory lymphoma, including those with limited options, such as PTCL. Even though the 2-year PFS and OS were lower for DLBCL (35%), it is noteworthy that these results are similar to those reported with alloSCT using matched sibling or unrelated donors and that patients with DLBCL relapsing after autologous SCT have a dismal outcome with very few other treatment options, although the use of chimeric antigen receptor T cells looks promising in this setting (Locke *et al*, 2018; Schuster *et al*, 2018).

In conclusion, using a large dataset of haploSCT with ptCy for lymphoma, we showed that the use of PBSC significantly improves engraftment but increases the risk of aGVHD. Conditioning had no effect on outcomes. The use of female donors in male patients, sisters or haplo-identical donors beyond first degree, increases the risk of cGVHD. These results provide critical information to help select the best donor in the setting of haploSCT for lymphoma. Of note, we found that PFS and OS are mostly influenced by disease characteristics (i.e., disease status and lymphoma subtype), whereas, with the exception of CMV compatibility or haplo-identical donors beyond first degree, no other donor characteristics (age, gender, relationship of donor to recipient, degree of HLA mismatch or ABO incompatibility, and prior pregnancy) had an impact on PFS or OS, supporting the selection of any first degree haplo-identical family member as a donor.

Author contribution

A.Ba. and A.S. proposed the study, interpreted the data and wrote the manuscript. S.M. and S.R. participated in study design, interpreted the data, and edited the manuscript. A.Bo. helped with the design and was responsible for statistical analysis. H.F. was the study coordinator. All other authors reported updated patient data, read and commented on the manuscript. All authors proofread the manuscript and agreed on the data presented.

Conflict of Interest

The authors declare no relevant conflict of interest.

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