

ARTICLE



Allogeneic hematopoietic stem cell transplantation from unmanipulated haploidentical donor and unrelated cord blood for T-cell lymphoma: a retrospective study from the Société Francophone de Greffe de Moelle et de Therapie Cellulaire

Jerome Cornillon ¹✉, Elisabeth Dagueuet ¹, Olivier Tournilhac², Didier Blaise ³, Stephanie NGuyen⁴, Helene Labussiere Wallet⁵, Patrice Chevallier⁶, Rémy Dulery ⁷, Edouard Forcade ⁸, Micha Srour⁹, Ali Bazarbachi ¹⁰, Nathalie Contentin¹¹, Bruno Lioure¹², Fabien Tinquaut¹, Claude-Eric Bulabois¹³, Marie-Therese Rubio ¹⁴, Marie Robin ¹⁵ and Jacques-Olivier Bay²

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After chemotherapy, fewer than 30% of patients with T-cell lymphoma (T-NHL) are long-term disease-free survivors. Thus, there is a growing interest in allogeneic stem cell transplantation (alloSCT) and its potential graft-versus-lymphoma effect (GVL) for patient with high-risk or recurrent T-NHL with the aim at providing durable disease control in T-NHL. We conducted this registry study to evaluate the outcome of recipients of alternative donor alloSCT for T-NHL. Patients transplanted with Haploidentical donor (Haplo, $n = 41$) or Umbilical Cord Blood (UCB, $n = 54$) were analyzed for overall survival (OS), non-relapse mortality (NRM), relapse, and acute/chronic graft-versus-host disease (aGVHD/cGVHD) incidence. At 2 years, OS and PFS were, respectively, of 59% and 53%, without significant difference between Haplo and UCB. In multivariate analysis, disease status at transplant was an independent risk factor for OS and PFS, and aGVHD III–IV was the main factor for OS and NRM. While no major impact of donor source on survival and mortality was noted, this study suggests that alternative donor transplantation appears feasible and offers benefits to patients with T-cell lymphoma.

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INTRODUCTION

T-cell non-Hodgkin's lymphoma (T-NHL) represents a heterogeneous group of lymphoma that contains more than 20 entities of mature T and Natural Killer (NK)-cell neoplasms. The World Health Organization (WHO) 2016 classification of hematologic malignancies defines T-NHL as lymphoid neoplasms originating from mature, post-thymic T lymphocytes [1]. T-NHL account for about 15% of all diagnosed NHL in Western countries while a higher prevalence is observed among Asian and Hispanic populations [2–4]. According to the revised WHO classification, follicular T-cell lymphoma (FTCL), including angioimmunoblastic T-cell lymphoma (AITL) and nodal T-cell lymphoma with a T follicular helper cell (Tfh) phenotype together with peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) are the most common subtypes, representing around 40% of T-NHL [4]. Except for anaplastic ALK+ lymphoma, T-NHL follows an aggressive clinical course with a poor response as compared to B-cell lymphomas, and optimal therapy remains challenging. While the impact of autoSCT in the first-line

setting is still debated [5–7], current guidelines recommend consolidation with first-line autologous SCT (autoSCT) after anthracycline-based multidrug chemotherapy for transplant-eligible patients [8–10]. The 5-year overall survival (OS) rate is estimated at around 40% in fit patients undergoing autoSCT with complete response (CR) or partial response (PR) after conventional chemotherapy and these patients exhibited long-term survival [11, 12]. Unfortunately, 30–40% of patients do not reach the point of autoSCT due to early disease progression and half of the patients who eventually receive consolidation with autoSCT will experience relapse [3, 7, 8].

Considering the worse prognosis of T-NHL and the potential graft-versus-T-cell lymphoma effect, allogeneic stem cell transplantation (alloSCT) has been often considered [13–15]. The role of alloSCT in the first remission is not ultimately clear, even if promising results on progression-free survival (PFS) and relapse rate were observed. These results are counterbalanced by a high level of toxicity due to graft-versus-host disease (GVHD) and a

¹Institut de Cancérologie Lucien Neuwirth, Saint-Priest-en-Jarez, France. ²CHU de Clermont-Ferrand, Clermont-Ferrand, France. ³Institut Paoli Calmettes, Marseille, France. ⁴Hopital La Pitie-Salpetriere, APHP, Paris, France. ⁵Hopital Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France. ⁶CHU de Nantes, Nantes, France. ⁷Hopital Saint-Antoine, APHP, Paris, France. ⁸CHU de Bordeaux, Bordeaux, France. ⁹CHRU de Lille, Lille, France. ¹⁰American University of Beirut, Beirut, Lebanon. ¹¹CHU de Rouen, Rouen, France. ¹²CHU de Strasbourg, Strasbourg, France. ¹³CHU de Grenoble, Grenoble, France. ¹⁴Hopital Brabois, Nancy, France. ¹⁵Hopital Saint-Louis, Paris, France. ✉email: jerome.cornillon@icloire.fr

higher level of non-relapse mortality (NRM) compared to autoSCT [7, 16, 17]. However, alloSCT has a strong role in the treatment of relapsed/refractory T-NHL. Across several studies, OS ranges between 31 and 50%, and PFS between 29 and 47% depending on histology and disease status at transplant [17]. According to an international consortium, recommendations are summarized into an algorithm that foresees autoSCT as a frontline consolidation in CR1/PR1 patients and alloSCT in relapsed sensitive patients even if autoSCT was previously performed [9].

The availability of HLA-matched sibling donor is limited and due to the risk of rapid progression of these aggressive T-NHL, in many cases, waiting on unrelated donor search may not be ideal. Therefore, alternative stem cell sources such as umbilical cord blood (UCB) or unmanipulated HLA-haploidentical blood or marrow have emerged as valuable strategies to alleviate the lack of compatible donors. Most studies suggest that the outcomes of patients after haploSCT or after conventional alloSCT are, at least, comparable [18–21]. To date, little is known regarding the use of alternative donor sources for T-NHL. Here, we report the clinical outcome of 95 patients T-NHL patients who received UCB or haploSCT.

MATERIALS AND METHODS

Study design and data collection

This is a retrospective registry-based, multicenter analysis. This study was approved by the SFGM-TC board and conducted in agreement with the declaration of Helsinki. Informed consent was obtained from all subjects. Clinical data were obtained through ProMISe (Project Manager Internet Server), from 36 Francophone centers. Eligibility criteria for this analysis only included T-NHL with mature T-cell phenotype, and who had received allogeneic SCT with cord blood ($n = 54$) or unmanipulated haploidentical stem cells ($n = 41$) between January 2003 and December 2017. Primary cutaneous T-cell lymphoma was distinct in the WHO classification and was excluded for data homogenization. Referring local physicians were asked to confirm the diagnosis, clinical history, treatment lines, and disease status at the time of SCT, data on the SCT, outcomes including GVHD grading and an updated follow-up.

Definitions

The histological diagnosis was based on referring local physicians. Disease status at transplantation was classified as complete remission (CR), partial response (PR), progressive disease or relapse as well as stable disease (SD). The local team according to the institutional standard of care assessed disease status.

Myeloablative conditioning (MAC) was defined as a regimen containing either total body irradiation (TBI) with a dose greater than 8 Gy, or a total dose of intravenous busulfan greater than 6.4 mg/kg. All other regimens were defined as reduced-intensity conditioning (RIC). Briefly, 65% of RIC Haplo patients and 75% of RIC UCB patients received a Baltimore regimen with Fludarabine 150 mg/m² (days –6 to –2), cyclophosphamide 29 mg/kg (days –6 to –5), and TBI of 2 Gy (day –1) [22]. Regarding the MAC group, the majority of patients received chemotherapy-based regimen (Thiotepa 10 mg/kg (days –6 to –5)), Busulfan 9.6 mg/kg (days –4 to –2), Fludarabine 150 mg/m² (days –4 to –2) or TBI-based regimen (cyclophosphamide 120 mg/kg (days –7 to –6)), TBI 12 Gy (days –5 to 0).

Neutrophil engraftment was defined as achieving absolute neutrophil count (ANC) $\geq 0.5 \times 10^9/L$ for three consecutive days, and platelet engraftment was defined as achieving platelet count $\geq 20 \times 10^9/L$ unsupported by platelet transfusions for 7 days. Acute GVHD (aGVHD) and chronic GVHD (cGVHD) were defined per published criteria [23, 24]. Full chimerism was defined as the presence of more than 95% unsorted donor cells at day +100 post-transplantation, and mixed chimerism was defined as between 5 and 94% recipient cells.

Statistical analysis

Endpoints included overall survival (OS), progression-free survival (PFS), non-relapse mortality (NRM), relapse incidence, and incidence of grades II–IV aGVHD and cGVHD. All outcomes were measured from the time of

alloSCT. OS was defined as death from any cause. PFS was defined as survival without lymphoma relapse or progression; patients alive without lymphoma relapse or progression were censored at the time of the last contact. The probabilities of OS and PFS were calculated by using the Kaplan–Meier method. Cumulative incidence functions were used to estimate NRM, relapse, and incidence of GVHD in a competing risk setting. Comparison of outcomes after transplant from different donors was performed with respect to OS, NRM, relapse, aGVHD, and cGVHD incidences. Median value and ranges were used for continuous variables and percentages as well as frequency for categorical variables. Statistical analyses were performed with SPSS as well as R software (3.2.5) and its associated packages.

RESULTS

Patients, donors, and transplant characteristics

Between 2003 and 2017, 95 patients were included in the analysis with a median age of 42.5 years (range 3.6–68); 65 (68%) were male. The study population was divided into two cohorts for analysis: Haplo ($n = 41$) and UCB ($n = 54$). Baseline patients-, disease-, and transplantation-related characteristics are summarized in Tables 1 and 2. Of the 95 patients, according to WHO 2015 classification, 38% had PTCL-NOS, 28% anaplastic large cell lymphoma (ALCL), 15% adult T-cell leukemia/lymphoma, 9.5% angioimmunoblastic T-cell lymphoma, and 7% extranodal NK/T-cell lymphomas. While most patients were in complete response (CR) or partial response (PR) before alloSCT ($n = 79$, 83%), 13 (14%) patients were in progressive disease (PD). The median time between diagnosis and alloSCT was 14.4 months (3.6–101).

The two groups were comparable with respect to diagnosis, history prior to alloSCT, and the median time from diagnosis to alloSCT. Around half of the patients completed at least three lines of treatment before transplantation ($n = 19$, 46.3% in Haplo group vs $n = 24$, 44.4% in UCB group), and one-third of patients underwent a previous autologous or allogeneic transplant (83.3% autologous vs 16.7% allogeneic transplant). Patients who underwent a second allogeneic transplant received either a matched or a UCB transplant as a first transplant. The UCB cohort was more likely to present as younger, compared to the Haplo cohort (33 years and 48.4 years respectively; $p = 0.019$). Of the Haplo group, 17% were female patients and 83% were male patients, whereas of the UCB group, 42.6% were female patients and 57.4% were male patients ($p = 0.008$). The graft source was peripheral blood stem cells (PBSC) in 33 (80%) patients in the Haplo group and in the UCB group, 29 (53.7%) patients received double units. All the haploidentical transplants received post-transplant cyclophosphamide. The conditioning regimen was myeloablative for 22% in Haplo vs 48.1% in UCB. Most of Haplo HSCT ($n = 39$, 95.1%) occurred since 2012.

Hematopoietic recovery and graft-versus-host disease

Engraftment by day 100 was successful in 89% of patients. Neutrophil recovery was achieved for 86 (90%) patients and platelets recovery more than 20 G/L for 77 (81%) patients, without difference between the two groups. The median time to neutrophil recovery was 19 days (range 12–31) in Haplo as compared to 25 days (range 6–44) in UCB ($p = 0.025$). Median time to platelet recovery was 22 days (range 7–47) in Haplo compared to 35 days (range 1–111) in UCB ($p < 0.001$). Eighty-five percent of tested patients had full donor chimerism on day 100. Primary or secondary graft failure was observed for 5 UCB patients (9%) and 3 Haplo patients (7%). Of note, 2 UCB patients underwent a second UCB transplantation and died from relapse and multi-organ failure, respectively. Incidence of aGVHD grades II–IV and grades III–IV was 37% (37% for Haplo; 37% for UCB) and 16% of patients (15% for Haplo; 17% for UCB), respectively on day 100. The rate of cGVHD and extensive cGVHD was 28% and 11%, respectively. No

Table 1. Patient demographics and clinical characteristics of 95 patients with T-cell lymphoma according to transplantation groups.

Characteristics	Total (N = 95)	Haplo (N = 41)	UCB (N = 54)	p-value
Patient age at treatment (years), median (min-max)	42.5 (3.6–68.4)	48.4 (10.9–68.4)	33 (3.6–65)	0.019
Gender of patients				0.008
Male	65	34 (83.0)	31 (57.4)	
Female	30	7 (17.0)	23 (42.6)	
Lymphoma WHO classification (2015)				0.416
Peripheral T-cell lymphoma, NOS	34 (35.7)	17 (41.5)	17 (31.5)	
Anaplastic large T-cell	27 (28.4)	8 (19.5)	19 (32.5)	
Adult T-cell leukemia/lymphoma	14 (14.7)	7 (17.0)	7 (13.0)	
Angioimmunoblastic T-cell lymphoma	9 (9.5)	6 (14.6)	3 (5.6)	
Extranodal NK/T-cell lymphoma, nasal type	7 (7.4)	2 (4.9)	5 (9.3)	
Enteropathy-associated T-cell lymphoma	2 (2.1)	1 (2.4)	1 (1.9)	
Hepatosplenic T-cell lymphoma	1 (1.1)	–	1 (1.9)	
Primary cutaneous anaplastic large cell lymphoma	1 (1.1)	–	1 (1.9)	
Median interval from diagnosis to transplantation, months (range)	14.4 (3.6–101)	15.4 (4.9–101)	14.2 (3.6–96.9)	0.58
Year of transplantation				<0.001
2003–2011	39 (41.1)	2 (4.9)	37 (68.5)	
2012–2017	56 (58.9)	39 (95.1)	17 (31.5)	
Number of lines before transplantation				0.77
1	19 (20.0)	9 (22.0)	10 (18.5)	
2	33 (34.7)	13 (31.7)	20 (37.0)	
3 or more	43 (45.3)	19 (46.3)	24 (44.4)	
Previous transplantation (n = 28)				0.22
Autologous	23 (24.2)	16 (39.0)	7 (13.0)	
Allogeneic	5 (5.3)	2 (4.9)	3 (5.6)	
Disease status at transplantation				0.40
CR	67 (70.5)	28 (68.3)	39 (72.2)	
PR	12 (12.6)	8 (19.5)	4 (7.4)	
Progressive disease or relapse	13 (13.7)	4 (9.8)	9 (16.7)	
Stable disease	3 (3.2)	1 (2.4)	2 (3.7)	

CR complete response, Haplo haploidentical stem cell transplantation, NOS not otherwise specified, PR partial response, UCB umbilical cord blood, WHO World Health Organization.

difference of all grades aGVHD or cGVHD incidence was noted between the two groups (Fig. 1).

Outcomes

The median of the follow-up was 21 months (0–152). It was longer for UCB than Haplo (42.5 vs 19 months, p 0.004). At the completion of the study, 30 patients had progression or relapse of the disease, without difference between UCB and Haplo. However, 29 patients (70%) after HaploSCT were alive at the final date in comparison to 26 patients (48%) for UCB (p 0.042) (Fig. 2a). Relapse was the leading cause of death for Haplo group, accounting for 9 cases (Fig. 2d). HSCT-related deaths accounted for only 3 patients (25%) in Haplo group and for 13 patients (52%) in the UCB cohort, suggesting that UCB transplantation is more toxic than Haplo. The main causes of death were infections (70% of cases), medication toxicities (15%), and GVHD (15%). OS and PFS were respectively of 59% and 53% at 2 years. OS and PFS trend to be better for Haplo, even if no statistical difference was noted (OS 71% vs 50%, p 0.056; PFS 63% vs 44%, p 0.063) (Fig. 2a, b). NRM was 23% for UCB vs 8% for Haplo (p 0.062) at the end of the study (Fig. 2c). NRM was higher if aGVHD II–IV was present

(29% vs 8.5%, p 0.013). No difference was observed regarding the intensity of the regimen or the presence of cGVHD.

Outcomes analysis is shown in Table 3. In univariate analysis, UCB trend to be worse in comparison with Haplo but not significant for OS (HR 1.83 (0.92–3.63), p 0.079), PFS (HR 1.79 (0.96–3.33), p 0.063) and NRM (HR 3.21 (0.9–11.41), p 0.057). In multivariate analysis, disease status at transplant (RC/PR vs other) is an independent risk factor for OS and PFS, and aGVHD III–IV is an independent factor for OS and NRM. UCB was associated with a higher risk for NRM (HR 3.42 (0.90–12.90), p 0.049).

DISCUSSION

Treatment of T-cell lymphoma remains complex because of a worse prognosis in comparison to B-cell lymphoma. Allogeneic HSCT is a frequently considered option in heavily pretreated patients, especially as a salvage strategy, including patients relapsing after a prior autologous HSCT [9]. In the literature, results for allogeneic SCT are comparable regardless of conditioning, donor source, and status at transplant, with 2-year OS ranging between 50 and 65% and 2-year PFS of about 50%

Table 2. Donor and transplant characteristics of 95 patients with T-cell lymphoma according to transplantation groups.

Donor and transplant characteristics	Haplo (N = 41)	UCB (N = 54)	p-value
ABO compatibility [missing]	[1]	[2]	0.320
Isogroup	26 (63.4)	24 (44.4)	
Bidirectional incompatibility	4 (9.8)	8 (14.8)	
Major incompatibility	4 (9.8)	6 (11.1)	
Minor incompatibility	6 (14.6)	14 (25.9)	
Cytomegalovirus status [missing]		[1]	0.10
D-/R-	14 (34.1)	18 (33.3)	
D-/R+	7 (17.0)	13 (24.1)	
D+/R-	4 (9.8)	12 (22.2)	
D+/R+	16 (39.0)	10 (18.5)	
Conditioning intensity			0.009
RIC	32 (78.0)	28 (51.9)	
MAC	9 (22.0)	26 (48.1)	
Donor to patient sex mismatch [missing]		[1]	0.484
Yes	25 (61.0)	36 (66.7)	
No	16 (39.0)	17 (31.5)	
Stem cell source			-
PBSC	33 (80.5)	-	
BM	8 (19.5)	-	
CB	-	54 (100)	
Graft composition			-
Total nucleated cells, median (range) ^a	7.2 (1.3–12.8)	2.6 (0.9–9.0)	
CD34 ⁺ cells, median (range) ^b	4.9 (0.8–16.0)	1.0 (0.8–6.0)	

D donor, Haplo haploidentical stem cell transplantation, MAC myeloablative-conditioning regimen, PBSC peripheral blood stem cells, R recipient, RIC reduced intensity conditioning regimen, UCB umbilical cord blood.

^a×10⁶/kg for Haplo, ×10⁷/kg for UCB.

^b×10⁶/kg for Haplo, ×10⁵/kg for UCB.

[25–30]. Yet, donor availability is a barrier for patients who lack an adequately HLA-matched and clinically suitable sibling donor. Moreover, response after relapse is generally short and HSCT procedure must be urgent. To fill the gap, alternative sources are supported in a number of reports, such as umbilical cord blood and partially HLA-matched family donors. In this manuscript, we report the outcomes of patients undergoing alloSCT with alternative donor sources specifically for T-NHL, a patient population that is at high risk of relapse. The main findings of our study are as follows: (i) HaploSCT or SCT with the cord blood in heavily treated patients, with a prior history of transplantation, resulted in prolonged OS and PFS (2-year OS 59%; 2-year PFS 53%) as median survivals were not reached with similar results as mentioned below; (ii) disease status at transplantation is the main factor influencing survival, (iii) the intensity of conditioning regimen did not have any impact on outcomes. As the choice of type of an alternative transplant can occur as a critical point in the

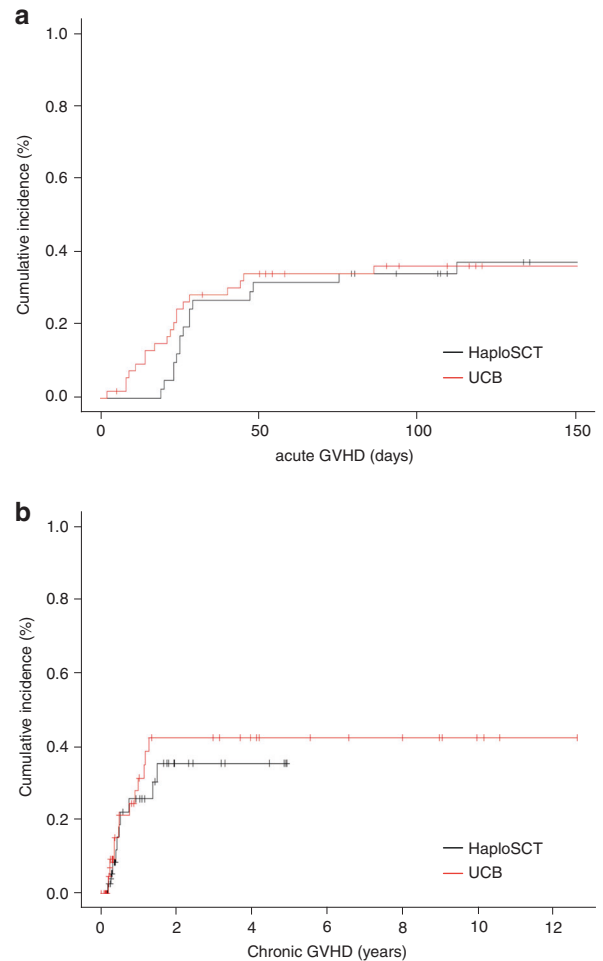


Fig. 1 Cumulative incidence of GVHD. Cumulative incidences of acute GVHD grades II–IV (a) and chronic GVHD (b) according to transplantation group (Haplo vs UCB) in 95 patients with T-cell lymphoma.

salvage treatment of T-cell lymphoma, we attempted to compare the results of the Haplo and the UCB groups. The value of comparison should be taken with caution considering the retrospective nature of the study, and a clear imbalance between the two groups in term of age, gender, and FU duration. We found a trend towards better OS and PFS as well as a lower NRM and a reduced death incidence in the Haplo cohort and HSCT-related deaths are higher in the UCB cohort.

To date, results from statistically powerful studies focusing on T-NHL are scarce. Indeed, most studies compared alternative donor, mainly haploidentical donor, to HLA-matched related or unrelated donor transplantation in adult patients with Hodgkin or NHL with no accurate information of T-cell subtypes. The Center for International Blood and Marrow Transplant Research (CIBMTR), based on a very large number of patients with Hodgkin and NHL, compared Haploidentical donor with either HLA-matched unrelated donor [20] or with HLA-matched related donor [19]; these data suggested that Haplo did not compromise outcome, with an additionally reduced rate of cGVHD [19]. Dodero et al., reported the long-term outcome of 52 patients receiving allogeneic SCT for relapsed/refractory peripheral T-cell lymphoma, including 6 haploidentical allografts [30]. Five-year OS and PFS of 43% and 24%, respectively, were achieved. A cumulative incidence (CI) of

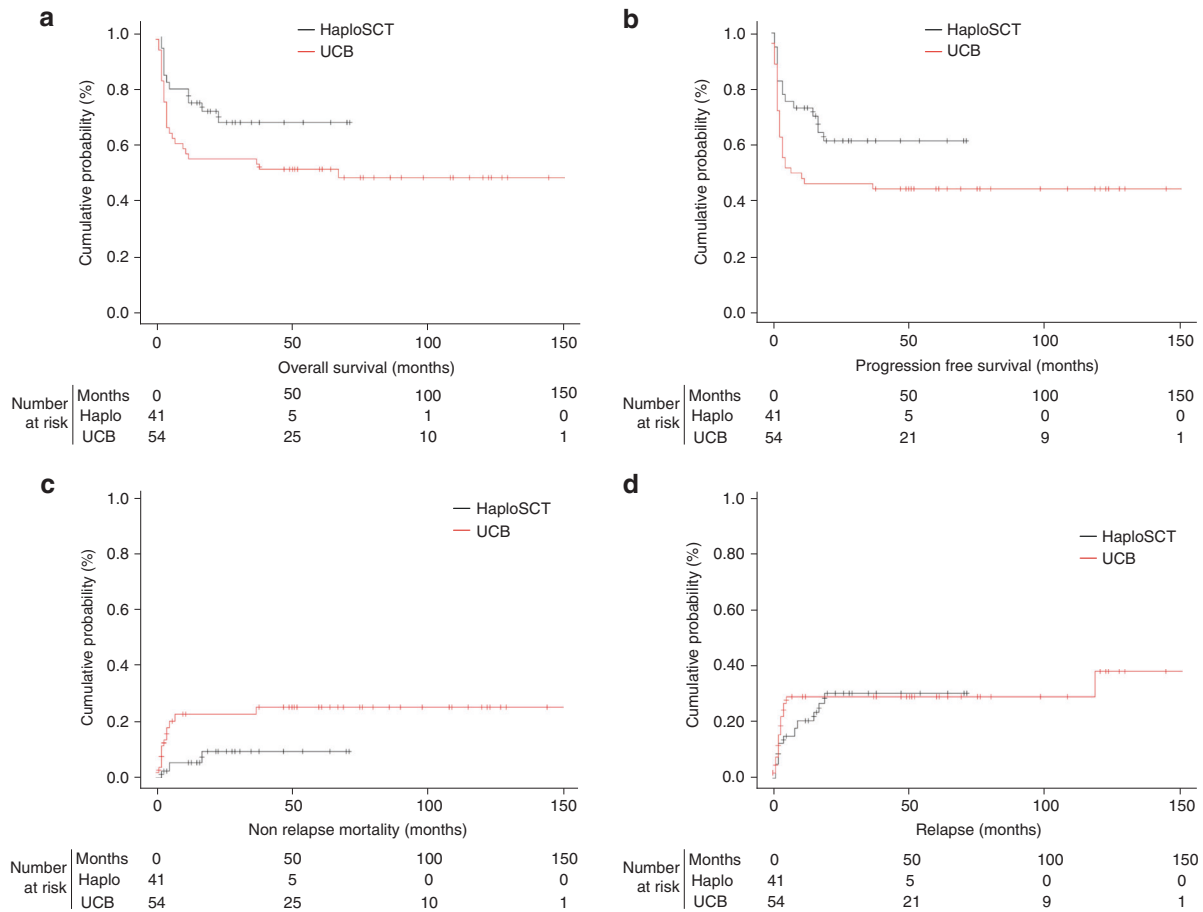


Fig. 2 Outcome after alloHSCT. Overall survival (a), progression-free survival (b), non-relapse mortality (c), and relapse (d) according to transplantation group (Haplo vs UCB) in 95 patients with T-cell lymphoma.

relapse of 59% was observed, as compared to 46% with HLA-matched sibling donors. The NRM (16%) as well as OS and PFS rates (59% and 53%, respectively) in the current analysis compare favorably against prior studies, in this heavily treated population. Indeed, the majority of patients had received two or more lines of treatment and one or two transplants before this transplant. Kanakry et al. described a cohort of 44 PTCL with 18 HaploRIC. Their results suggest a similar outcome in comparison to HLA-matched donor [31].

In the present study, unfortunately, we do not have precise data about donor lymphocyte infusion (DLI) whose impact could not be measured. While there is no possibility of DLI for UCB, DLI could be used as an opportunity to consolidate the response in HaploSCT, despite the high risk of GVHD. Even if differences were not statistically significant, we noticed a trend to better survival for HaploSCT. In particular, the difference between HaploSCT and UCB for which more HSCT-relative death was observed. NRM was higher in the UCB group (23% vs 8%, p 0.062), probably due to a higher rate of infections in this cohort as compared to HaploSCT and a potential deeper level of immunodepression. One missing parameter that could influence NRM is the sub-optimal dose of cord blood, for which we did not retrieve the graft composition. Yet, no difference in engraftment was observed between the two groups. No difference in aGVHD or cGVHD incidence was perceived between the two groups. Moreover, in a recent

retrospective study, Mamez et al., described the outcomes of a large cohort of PTCL after transplantation with related or unrelated matched donors. Results for OS and PFS are comparable with our data [25]. Finally, findings from the Fuchs et al. study demonstrate that haploidentical marrow over UCB transplantation using RIC conditioning resulted in lower NRM and superior OS in patients with chemotherapy-sensitive lymphoma or acute leukemia [32]. Overall, these findings and our study indicate that alternative donor transplantation, especially haploidentical donor, is a good alternative if necessary.

Similar to other registry-based analyses, there are some limitations to be considered such as the retrospective aspect of the study as well as the population size. Despite a short follow-up period, results are promising while further analysis with longer follow-up will be necessary to conclude with certitude. However, because of the events' kinetics in this population, few events are expected beyond two years as shown in the survival curves. Therefore, haploidentical donor or UCB donor seem good alternative sources of stem cells in the context of T-NHL allogeneic transplantation. The procedure is feasible with satisfactory results and with limited toxicity. Haploidentical donor should perhaps be considered as a better alternative source compared to cord blood because of less toxicity. A prospective study in comparison with other sources of graft is further expected to better define the place of these alternatives.

Table 3. Univariate and multivariate Cox analysis for progression-free survival, overall survival, and non-relapse mortality.

Covariates	Univariable HR (CI 95%)	p-value	Multivariable HR (CI 95%)	p-value
<i>Progression-free survival</i>				
Age at diagnosis	0.85 (0.46–1.57)	0.14	0.56 (0.25–1.22)	0.14
Year of transplantation				
2003–2011	1.00 (ref)	0.005	1.00 (ref)	0.002
2012–2017	0.43 (0.24–0.77)		0.36 (0.19–0.7)	
Lymphoma WHO classification		0.008		–
Anaplastic large T-cell	1.00 (ref)		–	
Adult T-cell leukemia/lymphoma	3.82 (1.66–8.81)		–	
Extranodal NK/T-cell lymphoma	2.42 (0.77–7.63)		–	
Enteropathy-associated T-cell lymphoma	1.91 (0.25–14.8)		–	
Peripheral T-cell lymphoma, NOS	1.14 (0.53–2.49)		–	
Angioimmunoblastic T-cell lymphoma	0.51 (0.11–2.28)		–	
Disease status at transplantation		0.001		0.007
CR/PR	1.00 (ref)		1.00 (ref)	
SD/PD	2.91 (1.52–5.56)		2.63 (1.36–5.08)	
HLA match		0.063		0.18
Mismatched relative (Haplo)	1.00 (ref)		1.00 (ref)	
Mismatched unrelated (UCB)	1.79 (0.96–3.33)		1.59 (0.80–3.17)	
Conditioning intensity				
RIC	1.00 (ref)	0.598	1.00 (ref)	0.12
MAC	0.85 (0.46–1.57)		0.98 (0.96–1.00)	
Number of lines before transplantation	0.91 (0.68–1.21)	0.93	–	–
aGVHD III–IV		0.109		0.01
No	1.00 (ref)		1.00 (ref)	
Yes	1.81 (0.89–3.65)		3.00 (1.38–6.52)	
<i>Overall survival</i>				
Age at diagnosis	0.99 (0.97–1.01)	0.16	0.98 (0.96–1.01)	0.17
Year of transplantation				
2003–2011	1.00 (ref)	0.025	1.00 (ref)	0.006
2012–2017	0.48 (0.26–0.91)		0.36 (0.17–0.76)	
Lymphoma WHO classification		0.013		–
Anaplastic large T-cell	1.00 (ref)		–	
Adult T-cell leukemia/lymphoma	4.33 (1.71–10.95)		–	
Extranodal NK/T-cell lymphoma	3.05 (0.91–10.18)		–	
Enteropathy-associated T-cell lymphoma	3.3 (0.41–26.61)		–	
Peripheral T-cell lymphoma, NOS	1.37 (0.57–3.32)		–	
Angioimmunoblastic T-cell lymphoma	0.72 (0.15–3.37)		–	
Disease status at transplantation		0.015		0.067
CR/PR	1.00 (ref)		1.00 (ref)	
SD/PD	2.27 (1.13–4.56)		2.04 (0.99–4.21)	
HLA match		0.079		0.23
Mismatched relative (Haplo)	1.00 (ref)		1.00 (ref)	
Mismatched unrelated (UCB)	1.83 (0.92–3.63)		1.57 (0.74–3.32)	
Conditioning intensity				
RIC	1.00 (ref)	0.694	1.00 (ref)	0.17
MAC	0.88 (0.46–1.69)		0.55 (0.24–1.30)	
Number of lines before transplantation	0.99 (0.73–1.33)	0.93	–	–
aGVHD III–IV		0.019		0.002
No	1.00 (ref)		1.00 (ref)	
Yes	2.32 (1.13–4.77)		4.23 (1.83–9.78)	

Table 3 continued

Covariates	Univariable HR (CI 95%)	p-value	Multivariable HR (CI 95%)	p-value
Relapse		0.049		–
No	1.00 (ref)		–	
Yes	2.03 (0.96–4.28)		–	
<i>Non-relapse mortality</i>				
Age at diagnosis	0.99 (0.97–1.02)	0.533	0.99 (0.95–1.02)	0.537
Year of transplantation				
2003–2011	1.00 (ref)	0.5	1.00 (ref)	0.02
2012–2017	0.68 (0.25–1.89)		0.23 (0.07–0.8)	
Lymphoma WHO classification		0.398		–
Anaplastic large T-cell	1.00 (ref)		–	
Adult T-cell leukemia/lymphoma	2.6 (0.63–10.64)		–	
Extranodal NK/T-cell lymphoma	1.32 (0.15–11.98)		–	
Enteropathy-associated T-cell lymphoma	5.57 (0.61–50.6)		–	
Peripheral T-cell lymphoma, NOS	0.78 (0.19–3.11)		–	
Angioimmunoblastic T-cell lymphoma	0.66 (0.07–5.95)		–	
Disease status at transplantation		0.916		–
CR/PR	1.00 (ref)		–	
SD/PD	0.92 (0.21–4.07)		–	
HLA match		0.057		0.049
Mismatched relative (Haplo)	1.00 (ref)		1.00 (ref)	
Mismatched unrelated (UCB)	3.21 (0.90–11.41)		3.42 (0.91–12.90)	
Conditioning intensity				
RIC	1.00 (ref)	0.344	–	–
MAC	0.58 (0.18–1.82)		–	
Number of lines before transplantation	0.91 (0.56–1.48)	0.693	–	–
aGVHD III–IV		<0.001		<0.001
No	1.00 (ref)		1.00 (ref)	
Yes	7.26 (2.63–20.07)		14.68 (4.27–50.98)	

CI confidence interval, CR complete response, aGVHD acute graft-versus-host disease, Haplo haploidentical stem cell transplantation, HR hazard ratio, MAC myeloablative conditioning, NOS not otherwise specified, PD progressive disease, PR partial response, RIC reduced intensity conditioning, SD stable disease, UCB umbilical cord blood, WHO World Health Organization.

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AUTHOR CONTRIBUTIONS

JC, ED, FT, and J-OB designed the research and/or analyzed the data. JC, ED, DB, SN, HLW, PC, RD, EF, MS, AB, NC, BL, C-EB, M-TR, MR, and J-OB collected the data. JC, ED, and FT performed the statistical analysis. JC and ED wrote the paper. All the authors approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to J.C.

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