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Allogeneic Stem Cell Transplantation in Mature T Cell and Natural Killer/T Neoplasias: A Registry Study from Spanish GETH/GELTAMO Centers

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A B S T R A C T

Despite advances in understanding the biology of mature T and natural killer (NK)/T cell neoplasia, current therapies, even the most innovative ones, are still far from ensuring its cure. The only treatment to date that has been shown to control aggressive T cell neoplasms in the long term is allogeneic stem cell transplantation (alloSCT). We aim to report the results of alloSCT for advanced mature T and NK/T neoplasias performed in centers from our national GELTAMO/GETH (Grupo Español de Linfoma y Trasplante de Médula Ósea/Grupo Español de Trasplante Hematopoyético y Terapia Celular) over the past 25 years. As a secondary objective, we analyzed the results of alloSCT from haploidentical donors. We performed a retrospective analysis of all patients who received an alloSCT in Spanish centers (n = 201) from September 1995 to August 2018. The 2-year overall survival (OS) and disease-free survival (DFS) were 65.5% and 58.2%, respectively. The univariate for OS and DFS showed statistically different hazard ratios for conditioning intensity, response pre-alloSCT, comorbidity index, donor/receptor cytomegalovirus

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status and Eastern Cooperative Oncology Group (ECOG) pre-alloSCT, but only a better ECOG pre-alloSCT remained significant in the multivariate analysis. There was an increased incidence of relapse in those patients who did not develop chronic graft-versus-host disease (GVHD) and an increased risk of death in those developing moderate to severe acute GVHD. The 1-year nonrelapse mortality was 21.9% and was mainly due to GVHD (30%) and bacterial infections (17%). When comparing unrelated donors with haploidentical donors, we found similar results in terms of OS and DFS. There was, however, a reduction of acute GVHD in the haploidentical group ($P = .04$) and trend to a reduction of chronic GVHD. In conclusion, alloSCT is the only curative option for most aggressive T cell neoplasias. Haploidentical donors offer similar results to related donors in terms of survival with a reduction of acute GVHD.

Mature T cell neoplasias constitute a highly heterogeneous group of entities characterized by an aggressive course in the majority of cases [1]. In recent years, there have been advances in the molecular profiling and in refining the classification of the most frequent categories of peripheral T cell lymphomas (PTCLs) [2]. Unfortunately, these advances are far from having led to a personalized therapeutic approach in the real world. Outside of the clinical trial setting and considering that a large proportion of patients relapse after high-dose chemotherapy followed by autologous stem cell rescue [3], allogeneic hematopoietic stem cell transplantation (alloSCT) is still the best therapeutic alternative in terms of efficacy, since it provides a long-term survival, free of lymphoma, for a significant proportion of patients with PTCL [4-12].

Results of alloSCT have improved over the past 2 decades, mostly due to reduction of nonrelapse mortality (NRM) due to reduction of severe graft-versus-host disease (GVHD) [13-15], introduction of better-tolerated conditioning regimens [16], and better opportunistic infection prevention [17] and treatment [18]. More recently, post-transplant cyclophosphamide (PTCy), initially developed for haploidentical alloSCT (haploSCT) [19-24], has been used for HLA-matched related donor (RD) and HLA-matched or 1-allele mismatched unrelated donor (UD) transplant protocols, leading to lower incidence of severe acute and chronic GVHD [25].

Despite the heterogeneity of patient characteristics and transplant platforms, most studies of alloSCT in lymphomas, and specifically in PTCL, have found that disease chemosensitivity and having a good performance status at alloSCT are strongly linked to improved survival [4-7]. In addition to other prognostic variables, it is important to emphasize that the potential impact of relatively new antilymphoma agents on post-alloSCT outcomes has not been studied to date; an important example is brentuximab vedotin, an important relatively recent therapeutic advance for $CD30^{+}$T cell lymphomas, or mogamulizumab for relapsed/refractory mycosis fungoides and Sézary syndrome. Experience with these drugs in Hodgkin lymphoma and adult T cell leukemia/lymphoma [26,27] has shown them to be effective therapies as a bridge to alloSCT.

We herein report the results of alloSCT for advanced mature T and natural killer (NK)/T neoplasias performed in centers from our national GELTAMO/GETH (Grupo Español de Linfoma y Trasplante de Médula Ósea/Grupo Español de Trasplante Hematopoyético y Terapia Celular) cooperative groups over more than 2 decades.

MATERIALS AND METHODS

Study Design

This is a retrospective, multicenter, registry-based analysis. The clinical information was extracted from the European Society for Blood and Marrow Transplantation registry through Project Manager Internet Server (ProMISe).

Eligibility criteria included patients older than 16 years with mature T cell neoplasias who received an alloSCT at GELTAMO/GETH centers. Additional variables and updated follow-up were obtained from investigators of each of the 20 participating centers by the study's main author (SN). The study was done in compliance with the Declaration of Helsinki and approved by research ethics committees and institutional review boards at each participating institution.

Procedures

Mature T cell neoplasias were characterized according to World Health Organization 2008 or 2016 classifications: nodal (peripheral T cell lymphoma, not otherwise specified; angioimmunoblastic T cell lymphoma, anaplastic large-cell lymphoma [all subcategories]), extranodal (primary cutaneous T cell lymphoma, extranodal NK T cell lymphoma, enteropathy-type T cell lymphoma; hepatosplenic $\gamma\delta$ T cell lymphoma; subcutaneous panniculitis-like T cell lymphoma), and less frequent T cell neoplasias (adult T cell leukemia/lymphoma, aggressive NK leukemia, and large granulocytic leukemia) were also registered. Diagnosis was performed by a local pathologist; we did not carry out a central pathologic review.

The study included alloSCTs performed from September 1995 to August 2018. The main additional variables requested were the international prognostic index, the prognostic index for T cell lymphomas, CD30 tumor expression, Epstein-Barr virus (EBV) positivity (Epstein-Barr encoding region (EBER) or LMP1), lines of therapy received (including the use of monoclonal antibodies), disease status, and updates on follow-up and patients' status.

Outcomes

The primary outcome was the 2-year overall survival (OS) after alloSCT. Secondary outcomes were 2-year progression-free survival (PFS), 1- and 2-year NRM, and day +90 and +12-month cumulative incidence of acute GVHD (aGVHD) and chronic GVHD (cGVHD), respectively.

OS was calculated from the date of transplantation until death or last follow-up. PFS was calculated from the date of transplantation until relapse or last disease-free follow-up. Relapse and death from any cause were considered events. NRM was defined as death without prior relapse. Neutrophil and platelet recovery were defined as achieving absolute neutrophil and platelet counts $\geq 0.5 \times 10^9$/L and 20×10^9/L, respectively, for 3 consecutive days. The diagnosis and grading of acute and chronic GVHD were performed by transplant centers using the standard criteria [28].

Statistical Analysis

Patient demographics and disease characteristics were described using median and range for continuous variables and counts and percentages for categorical variables. OS and PFS distributions were calculated with the Kaplan-Meier method.

Associations of patient covariates with outcomes were evaluated in univariate and multivariate analysis using a Cox proportional hazards model. All tests were 2-sided.

Variables (covariates) considered in the univariate analysis were patient age at transplantation, disease status at transplantation (chemosensitive versus chemorefractory), donor/recipient sex, type of conditioning previously defined [29] (reduced-intensity conditioning/myeloablative conditioning [RIC/MAC]), source of stem cells (peripheral blood [PB] stem cells versus bone marrow [BM] versus umbilical cord [UC]), patient/donor cytomegalovirus (CMV) serology, Eastern Cooperative Oncology Group (ECOG) performance status pre-alloSCT, and the hematopoietic cell transplantation comorbidity index (HCT-CI) at the time of transplantation.

Cumulative incidence functions were used to estimate relapse incidence and NRM in a competing risk setting, because death (without relapse) and relapse compete with each other. To study the potential effect of aGVHD and cGVHD on late post-transplant outcomes, landmark analyses were performed on day + 90 and +12 months, respectively. The cumulative incidence of aGVHD and cGVHD was also determined.

To compare the results of the more novel haploSCT platforms with PTCy versus UD 10/10 or UD 9/10, we restricted UD cases to the same period of time as haploSCT + PTCy cases (> year 2010) and compared the outcomes of these 2 alloSCT types. Fisher exact test was used to identify associations between categorical variables. Two-tailed *P*values of less than .05 were

considered statistically significant. The Mann-Whitney test was used to compare medians between groups.

Statistical analyses were done with SPSS: Armonk, NY: IBM Corp. IBM Corp. (version 26.0) and RStudio: RStudio, Boston, MA (version 1.2.1335) with package EZR version 1.42 [30].

RESULTS

The national registry included a total of 201 patients with mature T cell neoplasias who received an alloSCT from September 1995 to August 2018 (see Figure 1).

Patients' baseline lymphoma characteristics are summarized in Table 1.

The most frequent lymphomas were PTCL, not otherwise specified (41%; n = 82) and angioinmmunoblastic T cell lymphoma (22%; n = 43).

The median number of chemotherapy lines before alloSCT was 3 (1 to 7 lines), and 13.4% (n = 27) contained brentuximab vedotin in monotherapy (n = 19) or in combination (n = 8). Eighty-six percent (n = 173) were chemosensitive (complete response plus partial response), whereas 13.9% (n = 28) were chemorefractory (progressive disease or stable disease) before alloSCT. A total of 74 patients (182 cases with available information) had received an autologous SCT as a previous treatment before alloSCT (see Supplementary Table S1).

The median follow-up time of patients who had a transplant was 28 months (0 to 280), while the median follow-up of surviving patients at last follow-up was 49 months (range, 5 to 253 months).

The median age at alloSCT was 47 (17 to 69) years. Seventy percent (n = 121) of patients had an HCT-CI ≤2, and 94% (n = 179) of cases had an ECOG of 0 to 1 (see Table 2).

Sixty-six percent (n = 126) of alloSCTs were from RDs; of these, 68% (n = 86) were HLA identical, 28% were haploidentical (n = 35), 2 cases had a 1-HLA mismatched donor, and 3 cases had a syngeneic donor. Thirty-four percent (n = 66) of alloSCTs were from UDs: 89% (n = 59) were HLA identical, and 11% (n = 7) had a single mismatch. The information of donor and HLA typing from 9 patients was missing.

The stem cell source from related donors PB in 78 HLA-identical siblings, 2 mismatched siblings, 3 syngeneic donors, and 33 haploidentical donors; the source was BM in 8 HLA-identical siblings and in 2 haploidentical donors.

For UDs, the source was PB in 50 cases with HLA-identical donors and in 4 cases with mismatched donors; it was BM in 5 cases with HLA-identical donors and UC progenitors in 4 HLA-identical cases and 3 mismatched cases.

An RIC was used in 74% (n = 149) of patients and a MAC in 26% (n = 52).

Outcomes

The 2-year OS and PFS were 65.5% (95% confidence interval [CI], 58.3% to 71.7%) and 58.2% (95% CI, 50.9% to 64.8%) for the whole cohort, respectively. Patients with a syngeneic donor (n = 3) were excluded for the univariate and multivariate analysis. We did not find different outcomes between the most frequent histologic variants or GVHD prophylaxis

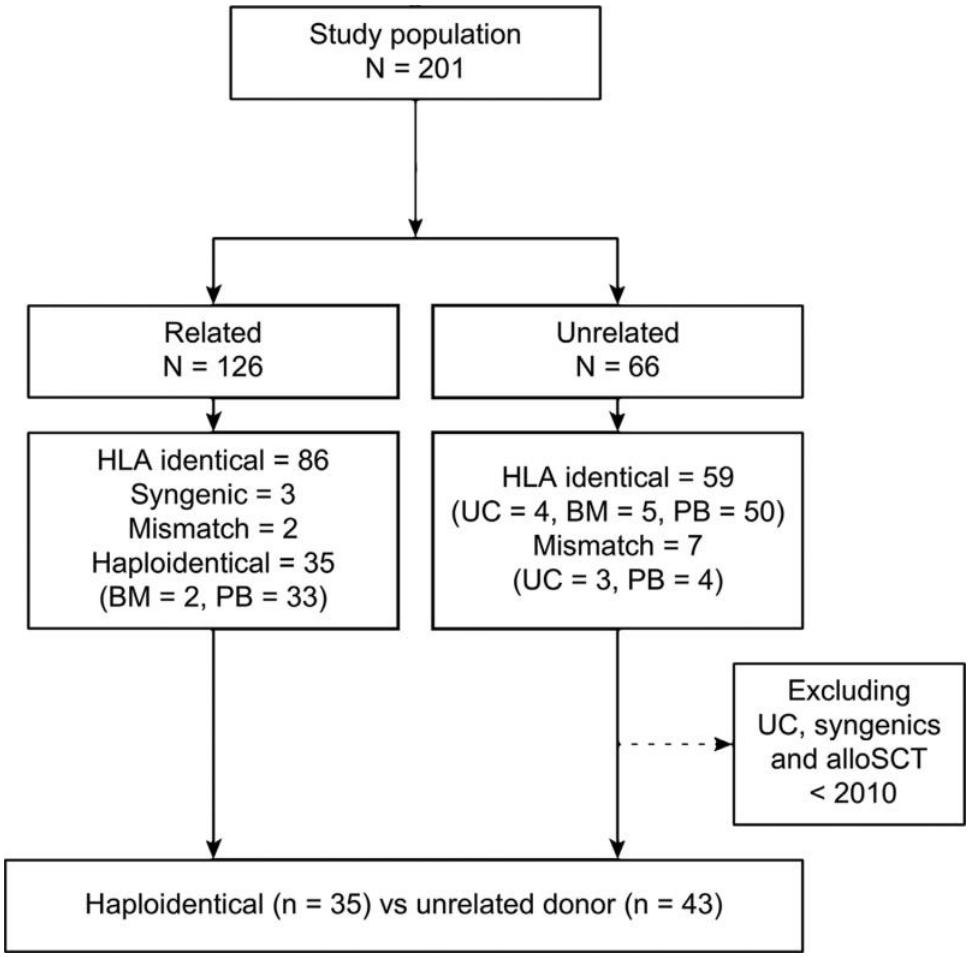

Figure 1. Study population.

Table 1
Patients' Baseline Lymphoma Characteristics

Characteristic	No. (%)
Sex	
Male	137 (68.2)
Female	64 (31.8)
Total	201 (100)
Age at diagnosis, median (range), y	45 (15-67)
Grouped diagnosis	
Nodal T cell lymphomas	148 (73.6)
Peripheral T cell lymphoma not otherwise specified	82
Angioimmunoblastic T cell lymphoma	43
Anaplastic large cell lymphoma ALK negative	16
Anaplastic large cell lymphoma ALK positive	7
Cutaneous T cell lymphomas	18 (9)
Mycosis fungoides	7
Primary cutaneous anaplastic large cell lymphoma	5
Sézary syndrome	4
Primary cutaneous angioimmunoblastic T cell lymphoma	1
Primary cutaneous gamma delta	1
Hepatosplenic T cell lymphoma	10 (5)
Adult T cell leukemia lymphoma	8 (4)
Extranodal NK/T cell lymphoma	13 (6.5)
Aggressive NK cell leukemia	2 (1)
Large granular lymphocyte leukemia	1 (0.5)
Enteropathy-associated T cell lymphoma	1 (0.5)
Total	201 (100)
ECOG at diagnosis	
ECOG 0-1	133 (82.7)
ECOG ≥2	28 (17.3)
Total	161 (100)
Stage at diagnosis	
Stages I-II	26 (13.3)
Stages III-IV	164 (86.8)
Total	189 (100)
B symptoms at diagnosis	
No B symptoms	84 (51.9)
B symptoms	78 (48.1)
Total	162 (100)
LDH (normal versus 1× UNL)	
Normal LDH	92 (70.2)
High LDH (1× UNL)	39 (29.8)
Total	131 (100)
Extranodal (1 vs >1)	
≤1 extranodal site	120 (62.2)
extranodal site	73 (37.8)
Total	193 (100)
IPI	
IPI 0-1	45 (40.5)
IPI 2-3	58 (52.2)
IPI 4	8 (7.2)
Total	111 (100)

LDH indicates lactate dehydrogenase; UNL, Upper normal limit; IPI, international prognostic index.

Table 2
Allogeneic Stem Cell Transplantation Information

Characteristic	No. (%)
Age at alloSCT, y	47 (17-69)
ECOG pre-alloSCT	
ECOG 0-1	179 (93.7)
ECOG 2-4	12 (6.3)
Total	191 (100)
Response pre-alloSCT	
Complete response	112 (55.7)
Partial response	61 (30.3)
Stable disease/progression	28 (13.9)
Total	201 (100)
HCT-CI	
HCT-CI 0-1	82 (47.7)
HCT-CI 2	39 (22.7)
HCT-CI 3	12 (7)
HCT-CI ≥4	39 (22.7)
Total	172 (100)
HLA compatibility	
Identical	145 (75.5)
Mismatch	9 (4.7)
Haploidentical	35 (18.2)
Syngeneic	3 (1.6)
Total	192 (100)
Source of stem cells	
Peripheral blood	179 (89.1)
Bone marrow	15 (7.5)
Umbilical cord	7 (3.5)
Total	201 (100)
Related versus unrelated	
Related	126 (65.6)
Unrelated	66 (34.4)
Total	192 (100)
CMV donor/receptor status	
Donor +/Receptor +	104 (55)
Donor +/Receptor −	9 (4.8)
Donor −/Receptor −	27 (14.3)
Donor −/Receptor +	49 (25.9)
Total	189 (100)
Conditioning intensity	
Reduced-intensity conditioning	149 (74.1)
Myeloablative conditioning	52 (25.9)
Total	201 (100)
Graft-versus-host disease prophylaxis	
Tacrolimus + sirolimus	42 (20.9)
MTX + CSA or tacrolimus	72 (35.8)
Cyclophosphamide	45 (22.4)
MMF + CSA or tacrolimus	28 (13.9)
ATG/alemtuzumab	11 (5.5)
None	3 (1.5)
Total	201 (100)
$CD34^+$ infused cells	5 (0.9-13.1)
Granulocyte graft days	16 (7-105)
Platelet graft days	14 (0-146)
Graft failure	3 cases

CMV indicates cytomegalovirus; MTX, Methotrexate; CSA, Cyclosporin A; MMF, mycophenolate mofetil; ATG, antithymocyte globulin.

regimens (analysis made with categories with >10 cases) (Figure 2a and b).

In all 198 cases, the univariate Cox regression analysis for OS showed statistically different hazard ratios (HRs) for type of conditioning (RIC versus MAC; HR, 2.1; 95% CI, 1.4 to 3.4; $P = .001$), type of response before alloSCT (chemosensitive versus chemorefractory; HR, 1.9; 95% CI, 1.1 to 3.2; $P = .025$), stem cell source (PB versus BM versus UC; HR, 1.7; 95% CI, 1.13 to 2.5; $P = .011$), $CD34^+$ cells infused ($\times 10^6$/kg) as a continuous

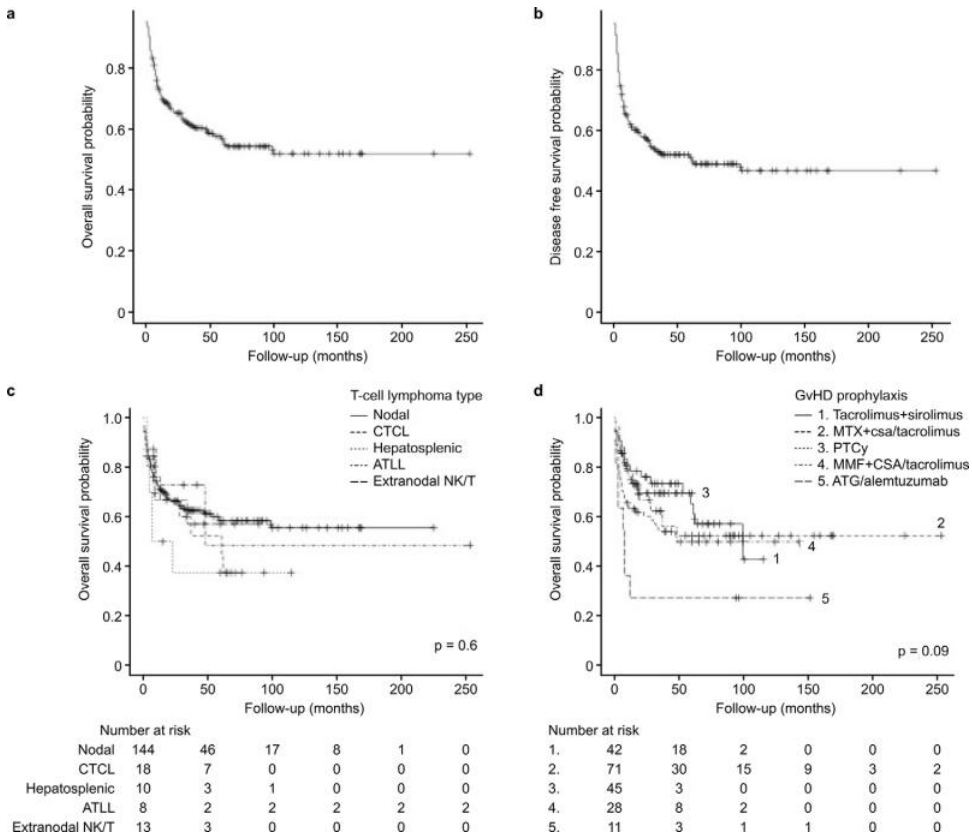

Figure 2. (a) Overall survival and (b) disease-free survival. (c) Overall survival by diagnosis. (d) Overall survival by graft-versus-host disease prophylaxis.

Table 3
Multivariate Cox Analysis for Overall Survival

Characteristic	HR	95% CI	*P* Value
HCT-CI	1.13	0.95-1.34	.2
Chemosensitive vs chemorefractory	1.3	0.69-2.46	.4
Age at alloSCT	0.98	0.97-1.00	.12
ECOG pre alloSCT	1.77	1.2-2.6	.004

variable (HR, 0.9; 95% CI, 0.8 to 1.0; $P = .028$), HCT-CI (0 to ≥4; HR, 1.2; 95% CI, 1.0 to 1.4; $P = .033$), donor/receptor CMV status (+/+, +/−, −/−, −/+) (HR, 1.2; 95% CI, 1.0 to 1.4; $P = .016$), and ECOG pre-alloSCT (HR, 1.9; 95% CI, 1.3 to 2.6; $P < .001$).

In the multivariate analysis, we excluded $CD34^+$ cells infused because it is correlated with the stem cell source (Kruskal-Wallis H test $P = .0001$). The only variable that remained significant in the multivariate Cox analysis was ECOG pre-alloSCT (see Table 3). The scaled Schoenfeld residuals showed no statistical results, indicating that the assumption of proportional hazards over time could be made.

The univariate Cox regression analysis of PFS showed statistically different HRs for type of conditioning (RIC versus MAC; HR, 1.8; 95% CI, 1.2 to 2.8; $P = .008$), $CD34^+$ cells infused ($\times 10^6$/kg) as a continuous variable (HR, 0.9; 95% CI, 0.8 to 1.0; $P = .036$), and ECOG pre-alloSCT (HR, 1.7; 95% CI, 1.2 to 2.3; $P = .001$).

We included ECOG pre-alloSCT and added the HCT-CI ($P = .09$), conditioning intensity ($P = .008$), and disease status pre-alloSCT ($P = .05$) for the multivariate analysis, and again the only variable that remained significant was the ECOG pre-alloSCT (see Table 4).

Table 4
Multivariate Cox Analysis for Disease-Free Survival

Characteristic	HR	95% CI	*P* Value
Conditioning intensity	1.59	0.95-2.67	.078
ECOG pre-alloSCT	1.5	1.02-2.19	.039
Chemosensitive vs chemorefractory	1.24	0.68-2.25	.5
HCT-CI	1.07	0.92-1.25	.4

Engraftment

There were 3 graft failures (2 in haploSCT and in 1 in HLA-identical RD). The median neutrophil and platelet engraftment times were 16 days (7 to 105) and 14 days (0 to 146), respectively.

Cumulative Incidence of Relapse and the Role of cGVHD

During follow-up, a total of 41 relapses were documented, and 25 patients died as a consequence of progressive disease. The 1-year cumulative incidence of relapse was 20.3% (95% CI, 14.1% to 26.1%), reaching a plateau at 26 months (24.2%; 95% CI, 17.3% to 30.5%). There were no differences in the cumulative incidence of relapse by occurrence of aGVHD. There was an increased incidence of relapse in those patients who did not develop cGVHD (analyzing cGVHD as a time-dependent covariate), 28.5% (95% CI, 18.9% to 37.0%; $P = .014$) versus mild (18.2%; 95% CI, 2.4% to 31.4%) and moderate to severe chronic GVHD (2.1%; 95% CI, 0% to 6.2%). No other variable had an impact on the cumulative incidence of relapse.

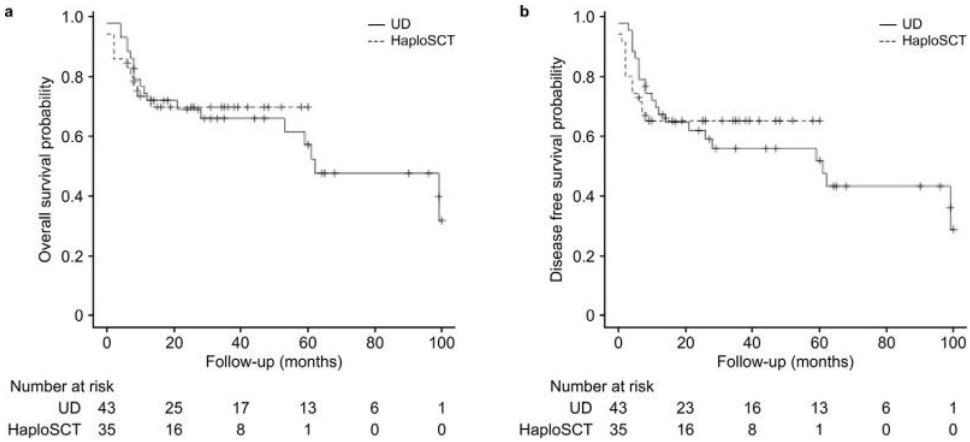

Figure 3. (a) Overall survival and (b) disease-free survival for unrelated donor and haploidentical donor.

Risk of Relapse after alloSCT Is Associated with Disease Status Pre- and Post-AlloSCT

As expected, disease status post-alloSCT (typically assessed around day +100) was conditioned by the disease status pre-alloSCT, and patients with chemosensitive disease pre-alloSCT had a 4.4-fold higher (95% CI, 1.6 to 12.6; $P < .001$) risk of having a complete or partial response after allo-SCT.

Applying binary logistic regression for the dependent variable relapse after alloSCT (n = 177) showed that patients with chemosensitive disease after alloSCT (around day +100) had a 4.8-fold higher (95% CI, 2.8 to 8.3; $P < .001$) risk of not progressing after alloSCT than those with chemorefractory disease.

GVHD and Its Impact on OS and PFS

In total, 107 of 191 (56%) evaluable patients developed aGVHD (40% grade I to II, 16% grade III to IV) and 76 (40%) of 190 developed cGVHD (15% mild and 25% moderate to severe). The cumulative incidence of aGVHD was 52.9% in the first 90 days (95% CI, 44.4% to 60.1%); for cGVHD, the incidence was 41.3% at 12 months (95% CI, 32.1% to 49.2%) with a plateau at 69 months (55.7%; 95% CI, 44.1% to 64.8%).

The day +90 OS landmark analysis for aGVHD showed that patients who did not develop aGVHD had a 1-year OS of 89.6% (95% CI, 79.5% to 94.9%), those with grades I to II had a 1-year OS of 78.8% (95% CI, 67.3% to 86.7%), and those who developed severe grade III to IV aGVHD had a much lower OS of 39.9% (95% CI, 22.2% to 57.1%) ($P < .001$). For cGVHD, the +12-month landmark analysis resulted in a 2-year post-alloSCT (1-year postlandmark point) OS of 89.5% (95% CI, 78% to 95.1%) for those without cGVHD, 91.7% for those with mild cGVHD, and 94.9% for those with moderate to severe cGVHD ($P = .841$).

The day +90 PFS landmark analysis for aGVHD showed a 1-year PFS probability for those who did not develop aGVHD of 87.1% (95% CI, 75.9 to 93.4), for those with grade I to II 84.8 % (95% CI, 73.5 to 91.5) and for those with severe grade III to IV 41.1%(95%CI, 23 to 58.8) ($P < .001$). As with OS, no differences in the 2-year PFS were found in the 1-year landmark analysis according to the development and severity of cGVHD.

In addition, in univariate Cox analysis, we did not identify any variables with an impact on the development of aGVHD or cGVHD (not even conditioning intensity or donor type).

NRM

There were 53 deaths related to transplant: 19 (36%) due to GVHD, 16 (30%) to bacterial infections, 9 (17%) to viral infections, 4 (7%) to sinusoidal obstructive syndrome, 3 (6%) to severe hemorrhage, and 2 (4%) to secondary neoplasia. The 1-year and 2-year incidence of NRM (competing risk with relapse) was 21.9% (95% CI, 14.79% to 28.38%) and 24% (95% CI, 16.97% to 31.34%).

The Cox univariate analysis showed that alloSCT with progenitors from UC had an increased risk of NRM compared with PB/BM (HR, 1.8; 95% CI, 1.0 to 3.1; $P = .039$), and patients who developed severe grade III to IV aGVHD also had an increased NRM (HR, 1.6; 95% CI, 1.0 to 2.4; $P = .032$). However, in multivariate analysis, both covariates showed only a nonsignificant trend ($P = .09$ and $P = .06$, respectively).

Haploidentical versus Unrelated Donor Transplant Recipients

To analyze the role of the 2 major alternative donor types currently used and include only the more recent cases (HLA-identical UD versus haploSCT), we selected patients who received the alloSCT after 2010. We had previously confirmed that, as expected, transplant outcomes were worse in patients who underwent transplantation before 2010 (see Supplementary Figure S1a), and in any comparison of more novel transplant strategies (haploSCT), one must select the control group (UD alloSCT) from the same most recent time period. There were differences in the baseline characteristics of the UD and haploSCT cohorts (see Supplementary Table S2).

The median follow-up time of survivors was 35 months: 40 months (8 to 100 months) in the UD group and 34 months (6 to 60 months) in haploSCT recipients, respectively.

The 1-year OS probability was 67.2% (95% CI, 51.0% to 79.1%) in the UD group and 65.2% (95% CI, 46.9 to 78.6) in haploSCT ($P = .9$). The 1-year PFS was 67.2% (95% CI, 50.99 to 79.1) and 65.2% (95% CI, 46.9 to 78.6), respectively ($P = .9$) (see Figure 3a and b).

Disease status pre-alloSCT violated the proportional hazard assumption in the univariate Cox regression analysis for all outcomes analyzed, but time-dependent separation into 2 post-transplant time periods by the estimated point of violation of the proportional hazards was not done, since multivariate analysis could not be done due to the small sample sizes and few events. Neither transplant type (main study variable) nor any other covariates had an impact on OS or PFS in univariate analysis (details not shown). The 1-year NRM was 25.3% (95% CI, 9.4% to 38.3%) for UD and 17.3% for haploSCT (95% CI, 20.99% to 30.1%), $P = .3245$. The cumulative incidence of aGVHD at 3 months was 64.7% (95% CI, 44.4% to 77.6%) and 39.3% (95% CI, 19.93% to 54.0%), respectively ($P = .040$), while

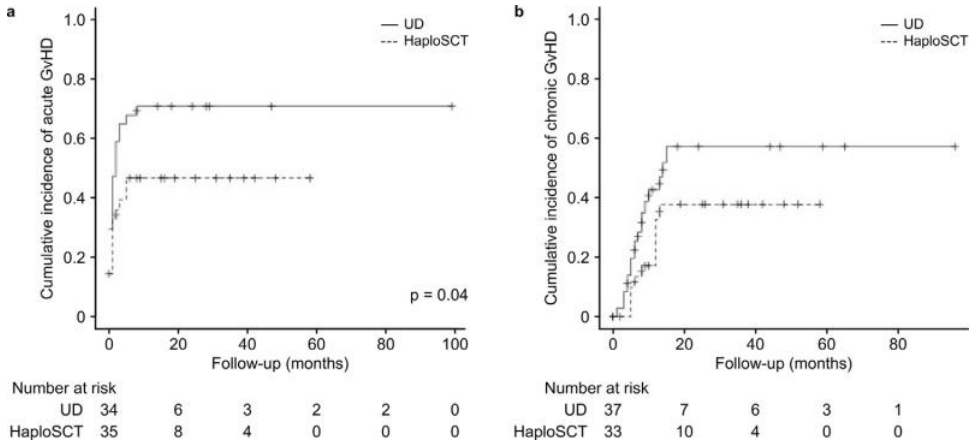

Figure 4. Cumulative incidence of (a) acute GVHD and (b) chronic GVHD for unrelated donor and haploidentical donor.

the incidence of cGVHD at 1 year was 42.6% (95% CI, 22.4% to 57.6%) and 32.6% (95% CI, 10.2% to 49.5%) (P = .1), respectively (see Figure 4a and b).

DISCUSSION

The complexity of mature T cell neoplasia classification, molecular profiling, and promising new therapies has been recently revised [31], and we are very aware that the current study includes a very heterogenous group of patients with a short-term dismal prognosis and very limited approved therapeutic approaches, making them optimal candidates for clinical trials. However, in this setting, clinicians are faced with the fact that alloSCT appears to be a real and feasible alternative that leads to a remarkably good OS and PFS at 3 and 7 years post-alloSCT (all around 50% in the current study). Of course, this is true only for relatively young "healthy" patients with a good performance status, whose PTCL or cutaneous T cell lymphoma is not in frank disease progression and with a significant proportion of cured patients having to live with the incapacitating spectrum of cGVHD. In our work, we grouped all mature T cell neoplasias due to their extreme rarity in alloSCT registries, and we focused on the alloSCT per se, which is common and more homogeneous irrespective of the histology. Although we did not find different outcomes by the histologic type, we are convinced that is due to small patient numbers, and future multinational studies with large enough patient numbers will surely find different outcomes for different PTCL/CTCL types.

As reported by other groups with sufficient follow-up, OS and PFS reach a plateau only after ~5 years after alloSCT [4]. We were able to identify the ECOG pre-alloSCT as the only independent prognostic variable for OS and PFS. Although we are convinced that many other variables do indeed have an independent impact, our database was unable to prove our convictions. On the bright side, preserving the patients' performance status before alloSCT is a reachable goal with the use of less toxic agents (brentuximab vedotin or mogamulizumab) when compared with conventional multiagent platinum-containing salvage chemotherapies.

The most surprising finding was that that chemosensitive disease did not remain significant in the multivariate analysis, although we are convinced that patients should reach alloSCT with their lymphoma clearly under control. Having chemosensitive disease pre-alloSCT reduced the risk of relapse at day +100, and being chemosensitive at day +100 also reduced the risk of later relapse; thus, it is only logical that chemorefractoriness is going to reduce survival, even if we were not able to "statistically" verify it. When we performed the same analysis exclusively for the most frequent T cell neoplasia (PTCL, not otherwise specified) (n = 79) chemosensitive/chemorefractory disease was the only variable that remained significant in the multivariate analysis for OS (P = .018) with an HR of 4.14 (95% CI, 1.27 to 13.46) and disease-free survival (P = .019) with an HR of 3.84 (95% CI, 1.25 to 11.82). This goes in line with recently published data [4] suggesting that our global analysis (including all pathologies) might be biased in the less frequent categories, and we are not adjusting all important factors that could impact the outcome; consequently, results should be interpreted cautiously.

In order to analyze whether aGVHD and cGVHD had an impact on improving the outcome of patients with chemorefractory disease at alloSCT, we analyzed their impact, first as time-dependent covariates, and later as landmark analysis on day +90 and month +12 for aGVHD and cGVHD, respectively. However, to our surprise, the outcomes of both chemosensitive and chemorefractory patients were not impacted by the development of GVHD.

This is a very interesting result highlighting the potential role of a graft versus T cell lymphoma effect in the absence of GVHD, especially cGVHD, and whether the introduction of PTCy outside of haploSCT may partially explain this observation [23]. However, as in most prior studies, the development of cGVHD reduced the risk of relapse [32].

Although the samples were statistically small, an important objective for us was comparing the results of haploSCT + PTCy with HLA-identical UD transplants. However, our early comparative results show no differences in terms of OS and PFS. There was, however, a reduction of aGVHD in haploSCT recipients (P = .04) and trend to a reduction of cGVHD. We are convinced these differences are due to the universal use of PTCy in haploSCT recipients and are currently studying its incorporation in all types of alloSCT in lymphoma.

These results open the possibility to avoid overtreating refractory patients waiting for a better-matched unrelated donor when an haploidentical donor is available and, maybe in the future, allow proceeding to an alloSCT in earlier disease stages [24,32].

AlloSCT is the only curative option for most T cell neoplasias relapsing after autologous stem cell rescue, demonstrated

by a 2-year OS and PFS of 66% and 58%, respectively, and the performance status pre-alloSCT is the most relevant predictor of OS and PFS. Patients who do not develop cGVHD have an increased risk of relapse, and those who develop aGVHD have an increased NRM. Our preliminary results showed similar OS and PFS for haploidentical and unrelated donors. The use of PTCy probably explains the reduced risk of aGVHD in the haploSCT group, and this is a current area of research in alloSCT from HLA-identical donors.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jtct.2021.03.014.

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