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ARTICLE

Allogeneic stem cell transplantation as a curative option in relapse/refractory diffuse large B cell lymphoma: Spanish multicenter GETH/GELTAMO study

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Abstract

We performed a retrospective multicenter study including 140 patients with relapsed/refractory (R/R) diffuse large B cell lymphoma (DLBCL) who underwent allogeneic hematopoietic stem cell transplantation (allo-SCT) from March 1995 to November 2018. Our objective was to analyze long term outcomes. Seventy-four percent had received a previous auto-SCT (ASCT) and the median number of lines pre-allo-SCT was 3 (range 1–9). Three year-event free survival (EFS) and overall survival (OS) were 38% and 44%, respectively. Non-relapse mortality (NRM) at day 100 was 19%. Cumulative incidence of grade III–IV acute graft versus host disease (GVHD) at day 100 was 16% and moderate/severe chronic GVHD at 3 years 34%. Active disease at allo-SCT (HR 1.95, $p = 0.039$) (HR 2.19, $p = 0.019$), HCT-CI ≥ 2 (2.45, $p = 0.002$) (HR 2.33, $p = 0.006$) and donor age >37 years (HR 2.75, $p = 0.014$) (HR 1.98, $p = 0.043$) were the only independent variables both for PFS and OS, respectively. NRM was significantly modified by HCT-CI ≥ 2 (HR 4.8, $p = 0.008$), previous ASCT (HR 4.4, $p = 0.048$) and grade III–IV acute GVHD on day 100 (HR 6.13, $p = 0.016$). Our data confirmed that allo-SCT is a curative option for patients with R/R DLBCL, displaying adequate results for fit patients with chemosensitive disease receiving an allo-SCT from a young donor.

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Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL). Although it is a curable disease, up to 30–40% of DLBCL patients will experience relapse/progression (R/R). For fit patients with R/R DLBCL experiencing a response to salvage treatment, high-dose chemotherapy and autologous stem cell transplantation (ASCT) has been the standard of care [1]. The SCHOLAR-1 retrospective study defined a refractory population that included progressive or stable disease as best response at any point during chemotherapy (>4 cycles of first-line or 2 cycles of later-line therapy) or relapsed ≤12 months of ASCT [2]. For these patients with refractory DLBCL, the objective response rate was 26% (complete response 7%) to the next line of therapy, and the median overall survival (OS) was 6.3 months. Therefore, for subjects who experience early relapse after ASCT or for whom ASCT is not an option because the NHL is not sufficiently chemosensitive, better approaches are needed.

Allogeneic (allo)-SCT may be a curative option with the advantage of a tumor-free graft and the benefit of a graft-versus-lymphoma (GVL) effect. This GVL effect has been well demonstrated by the fact that some patients who experience relapse after ASCT will be cured with allo-SCT. However, its efficacy could be limited by high non-relapse mortality (NRM) due to toxicity of conditioning regimen, graft-versus-host disease (GVHD) and infections complications, especially in heavily pre-treated patients. Despite such limitations, in the literature there is a consistent message that long-term OS in 20–50% is possible [3–5].

Recent approval of CART therapy for patients with R/R DLBCL after at least two lines of therapy has established a possible curative option for these patients [6, 7]. There is emerging uncertainty whether there is still a role for allo-SCT in the treatment of R/R DLBCL [8] due to the favorable outcome data reported for CART therapy. Therefore, our objective was to analyze long term follow up in patients receiving allo-SCT and try to define the optimal role of allo-SCT in R/R DLBCL in the CAR-T era.

Patients and methods

Patient eligibility

We performed a retrospective multicenter study including patients from centers of GETH/GELTAMO with R/R DLBCL who underwent allo-SCT from March 1995 to November 2018. The histological diagnosis was based on local review, and patients were staged according to the Ann Arbor system. Disease status at allo-SCT was classified as complete remission (CR), partial response (PR), or active disease defined as primary refractory, chemoresistant relapse, stable disease and progressive disease. Disease status was assessed by the local team according to the Revised Response Criteria for Malignant Lymphoma [9] and/or Lugano Classification [10] and to the institutional standard of care. Myeloablative conditioning was defined as a regimen containing either total body irradiation (TBI) with a dose >6 Gy, a total dose of oral busulfan >8 mg/kg, or a total dose of intravenous busulfan >6.4 mg/kg. All other regimens were defined as reduced intensity conditioning (RIC) [11]. The diagnosis and grading of acute [12, 13] and chronic graft versus host disease GVHD [14] (aGVHD and cGVHD) was performed by the centers using the standard criteria. Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) was considered as previously defined [15–17]. Informed consent for transplantation and data collection was obtained locally according to regulations applicable at the time of transplantation.

Outcome measures

All outcome measures were assessed from the time of allo-SCT. Event-free survival (EFS) was defined as the time from allo-SCT to relapse, progression or death from any cause. OS was defined as the time from allo-SCT to death from any cause and surviving patients were censored at last follow-up. Non-relapse mortality (NRM) was defined as the time from allo-SCT to death without previous disease relapse or progression. Cumulative incidence (CI) of relapse was defined as the time from allo-SCT to relapse or progression. GVHD-free/relapse-free survival (GRFS) was defined as the time from allo-SCT to relapse, progression, death, grade III–IV aGVHD and/or moderate-severe cGVHD [18].

Statistical analysis

Qualitative or binomial variables were expressed as frequencies and percentages. The binary logistic regression was used to find out the risk factors associated with NRM or GVHD. Time to event variables were estimated according to the Kaplan–Meier method and comparisons between variables of interest were performed by the log-rank test. Progression-free survival was defined as the time from transplantation to disease progression, death of any cause or last follow-up. Variables included in the univariate analysis were interval between diagnosis and allo-SCT, period of transplant, donor type, number of lines prior to allo-SCT, previous ASCT, HCT-CI, disease status at allo-SCT, conditioning type, GVHD prophylaxis, stem cell source, patient and donor age, donor sex, CMV status, response rate on day 100, acute GVHD on day 100 and chronic GVHD at 3 years. To obtain the most discriminative cutoff for patient

and donor age we used Receiver Operating Characteristic (ROC) curves for the event progression or death of any cause and cord bloods were excluded. Multivariate analysis with the variables that appeared to be significant in the univariate analysis was carried out according to the Cox proportional hazard regression model. For those variables not available at the moment of transplantation, acute or chronic GVHD, a Landmark analysis was performed. To elaborate the prognostic score, we consider only those variables available at the time of transplantation that showed an independent prognostic role for progression-free survival. All p values reported were 2-sided, and statistical significance was defined at $p < 0.05$.

Results

One-hundred and forty patients diagnosed of DLBCL [41% male, median age at diagnosis 45 years (14–66)] fulfilled the inclusion criteria. Lymphoma characteristics at diagnosis are summarized in Table 1. Median time between diagnosis and allo-SCT was 26 months (6–174). Seventy-four percent had received a previous ASCT and the median number of lines pre-allo-SCT were 3 (1–9). The allo-SCT characteristics are summarized in Table 2.

Response rate

Overall and complete response rate on day 100 were 72% and 68%, respectively. Among those patients who underwent allo-SCT in CR, 92% maintained RC, 1% PR and 7% progressed. For patients in PR at allo-SCT, 61% achieved CR on day 100, 9% continued in PR and 30% progressed. Regarding patients with active disease at allo-SCT, 54% achieved CR and 46% did not show any response.

NRM and relapse/progression

NRM rate was 19% (95%CI 11–24) on day 100 and 30% (95%CI 23–39) at 1 year (Fig. 1a). NRM was influenced by patient age >37 years [RR 1.03 (95% CI 1–1.06), $p = 0.044$], HCT-CI ≥ 2 [RR 4.13 (95% CI 1.81–9.46), $p = 0.001$], interval from diagnosis to allo-SCT > 26 months [RR 2.72 (95% CI 1.34–5.53), $p = 0.006$], previous ASCT [RR 3.69 (95% CI 1.48–9.18), $p = 0.005$], donor age >37 years [RR 3.2 (95% CI 1.48–6.94), $p = 0.003$] and aGVHD on day 100 [RR 4.98 (95% CI 1.92–12.92), $p = 0.001$]. In multivariate analysis, NRM was independently influenced by HCT-CI ≥ 2 [(HR 4.8 (IC95% 1.51–15.4), $p = 0.008$], previous ASCT [(HR 4.4 (IC95% 1.01–18.9), $p = 0.048$] and acute GVHD grade III–IV [(HR 6.13 (IC95% 1.4–26.8), $p = 0.016$] (Table 3). After a median follow-up of 53 months (8-210), 42% of the patients were alive and 91% of them were free of disease with a CI of relapse of 32% (95% CI 23–41) and 35% (95% CI 25–45) at 1 and 3 years, respectively (Fig. 1b).

Table 1 DLBCL characteristics at diagnosis ($n = 140$).

	N (%)
Age at diagnosis (median, range), years	45 (14–66)
Sex (M/F)	58 (41%)/82 (59%)
ECOG	
0–1	91 (65%)
>1	21 (15%)
Missing	28 (20%)
Ann Arbor stage	
I–II	26 (19%)
III–IV	110 (79%)
Missing	4 (3%)
B symptoms	
Yes	51 (36.5%)
No	65 (46.5%)
Missing	24 (17%)
CNS involvement	
Yes	6 (4.25%)
No	128 (91.5%)
Missing	6 (4.25%)
Bone marrow involvement	
Yes	38 (27%)
No	98 (70%)
Missing	4 (3%)
Extranodal site	
0–1	82 (58.5%)
>1	51 (36.5%)
Missing	7 (5%)
LDH	
Normal	30 (21%)
High	61 (44%)
Missing	49 (35%)
Beta-2-microglobulin	
Normal	36 (26%)
High	39 (28%)
Missing	65 (46%)
Bulky mass	
Yes	94 (67%)
No	42 (30%)
Missing	4 (3%)
IPI	
0–1	25 (18%)
>1	55 (39%)
Missing	60 (43%)
Diagnosis	
DLBCL NOS	127 (91%)
Double hit	7 (5%)
Double expressor	2 (1%)
Others	4 (3%)

M Male, *F* Female, *ECOG* Eastern Cooperative Oncology Group, *CNS* Central nervous system, *LDH* Lactate dehydrogenase, *IPI* International Prognostic Index, *DLBCL* Diffuse large B cell lymphoma, *NOS* Not otherwise specified.

Table 2 Allo-SCT characteristics.

	$N = 140$
Age at allo-SCT (median, range), years	47 (14–72)
Time from diagnosis to allo-SCT (median, range), months	26 (6–174)
Number of lines prior to allo-SCT (median, range)	3 (1–9)
Previous ASCT	103 (74%)
Time from ASCT to allo-SCT (median, range), months	15 (3–115)
HCT-CI	
0–1	54 (39%)
2	30 (21%)
≥3	26 (19%)
Missing	30 (21%)
Disease status at allo-SCT	
Complete response	77 (55%)
Partial response	40 (29%)
Active disease	17 (12%)
Missing	6 (4%)
Stem cell source	
Peripheral blood	122 (87%)
Bone marrow	8 (6%)
Cord blood	8 (5%)
Peripheral blood + Cord blood	2 (1%)
Donor type	
HLA-identical sibling	72 (51%)
Mismatched sibling donor	2 (1%)
Matched unrelated	25 (18%)
Mismatched unrelated	6 (4%)
Haploidentical	25 (18%)
Cord blood/Haplo-cord	10 (7%)
Conditioning regimen	
Reduced intensity conditioning	111 (79%)
Flu-Mel	65 (59%)
Flu-Bu	18 (16%)
Flu-Bu-Cy	7 (6%)
Flu-Bu-TT	5 (5%)
Others	16 (14%)
Myeloablative	29 (21%)
Flu-Bu-TT	9 (31%)
BEAM	7 (24%)
TBI-Cy	5 (17%)
Flu-Bu-Cy	2 (7%)
Flu-Bu	1 (3%)
Others	5 (17%)
GvHD prophylaxis	
Cyclosporine-Methotrexate	40 (29%)
Cyclosporine-Micophenolate mofetil	30 (21%)
Tacrolimus-Sirolimus	24 (17%)
Post-transplant Cyclophosphamide	26 (19%)
Timoglobulin based prophylaxis	17 (12%)
Others	3 (2%)
Donor age (median, range)	40 (12–69)
Donor sex	
Male	82 (58.5%)
Female	57 (41%)
Missing	1 (0.5%)
CMV status	
R+/D+	60 (43%)
R+/D−	41 (29%)
R−/D+	15 (11%)
R−/D−	18 (13%)
Missing	6 (4%)
CD34 + infused (median, range)	5.5 (0.4-14)
Median >20,000/mm3 platelets recovery (days, range)	14 (12–16)
Median >500/mm3 neutrophils recovery (days, range)	15 (14–16)

ASCT Autologous hematopoietic stem cell transplantation, *HCT-CI* hematopoietic cell transplantation-specific comorbidity index, *Flu* Fludarabine, *Mel* Melphalan, *TT* Thiotepa, *Cy* Cyclophosphamide, *R* Receptor, *D* Donor.

Survival analysis

One and 3-year-EFS were 49% (95% CI 45–54) and 38% (95% CI 34–43), respectively (Fig. 2a). EFS was influenced by active disease at allo-SCT, HCT-CI ≥ 2, patient and donor age >37 years, being transplanted before 2015, active disease on day 100, acute grade III–IV GVHD on day 100 and chronic severe GVHD at 3 years (Table 4). Disease status at allo-SCT was evaluated by PET/CT in 73% of the patients and there were no differences on EFS between patients with PR and CR in this specific subgroup. In the multivariate analysis active disease at allo-SCT [(HR 1.95 (IC95% 1.04–3.69), $p = 0.039$], HCT-CI ≥ 2 [(HR 2.45 (IC95% 1.37–4.36), $p = 0.002$] and donor age >37 years [(HR 2.75 (IC95% 1.56–4.86), $p = 0.014$] were the only variables independently associated to a worse EFS (Table 3).

One and 3-year-OS were 56% (IC95% 51–60) and 44% (IC95% 40–48), respectively (Fig. 2b). OS was influenced by active disease at allo-SCT, HCT-CI ≥ 2, patient and donor age >37 years, stem cell source, being transplanted before 2015, active disease on day 100, acute grade III–IV GVHD on day 100 and chronic severe GVHD at 3 years (Table 4). In the multivariate analysis active disease at allo-SCT [(HR 2.19 (IC95% 1.14–4.23), $p = 0.019$], HCT-CI ≥ 2 [(HR 2.33 (IC95% 1.28–4.24), $p = 0.006$] and donor age >37 years [(HR 1.98 (IC95% 1.02–3.84), $p = 0.043$] were

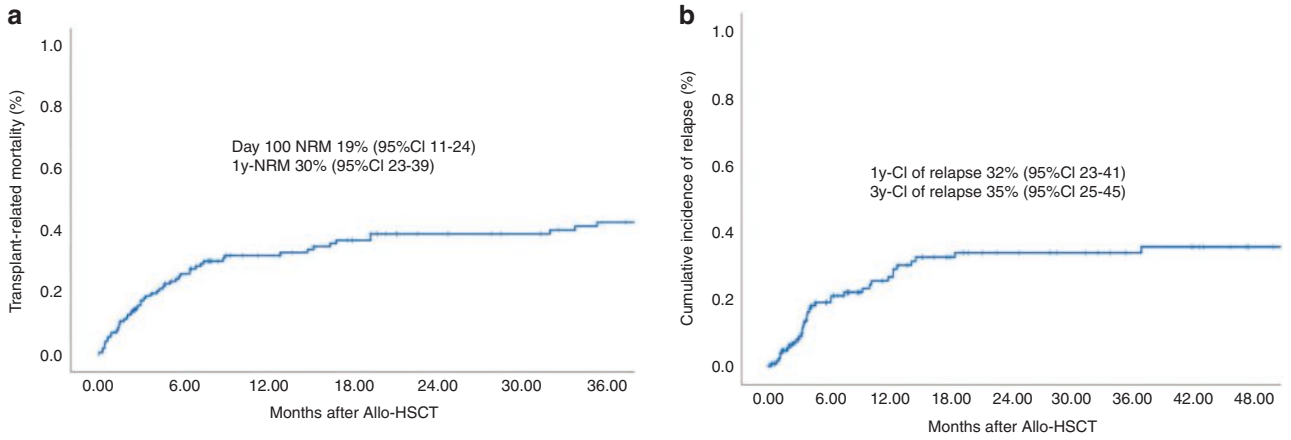

Fig. 1 Survival analysis in total cohort. CI of relapse (**a**) and NRM (**b**).

Table 3 Multivariate analysis.

	EFS (HR, 95% CI)	*p*	OS (HR, 95% CI)	*p*		NRM (HR, 95% CI)	*p*
Active disease at allo-SCT	1.95 (1.04–3.69)	**0.039**	2.19 (1.14–4.23)	**0.019**	HCT-CI ≥ 2	4.8 (1.51–15.4)	**0.008**
HCT-CI ≥ 2	2.45 (1.37–4.36)	**0.002**	2.33 (1.28–4.24)	**0.006**	Previous ASCT	4.4 (1.01–18.9)	**0.0048**
Donor age > 37 years	2.75 (1.56–4.86)	**0.014**	1.98 (1.02–3.84)	**0.043**	Grade III–IV aGVHD on day 100	6.13 (1.4–26.8)	**0.016**

Bold values indicate statistical significance.

EFS Event free-survival, *OS* Overall survival, *HR* Hazard ratio, *CI* Confidence interval.

the only variables independently associated to a worse OS (Table 3). Causes of death were NRM in 51 (63%) of the patients [of them 53% were infections, 27% GVHD, 12% infections and GVHD concomitantly and 8% veno-occlusive disease], disease progression in 26 (32%) and 4 (5%) others.

Based on these three risk factors independently significant both for EFS and OS in the multivariate analysis (active disease at allo-SCT, HCT-CI ≥ 2 and donor age >37 years) a risk score was elaborated. All the patients with these three factors available were included ($N = 91$). Each variable was scored with 1 point considering a similar HR for all of them. Three risk groups were formed on the basis of the shape of the Kaplan–Meier curves for PFS: 0 [18 (20%)], 1 [39 (43%)] and 2–3 factors [34 (37%)]. One and 3y-EFS was 83% with 0 factors both at 1 and 3 years compared to 59% and 49% with 1 risk factor [HR 4.1 (95% IC 1.2–14] and 26% and 12% with 2–3 risk factors [HR 11.4 (95% IC 3.5–37.7], respectively ($p < 0.001$) (Fig. 3a). This score also showed 3 groups for 1 and 3-year-OS: 89% with 0 both at 1 and 3 years compared to 66% and 50% with 1 risk factor [HR 6.1 (95% IC 1.4–26] and 29% and 18% with 2–3 risk factors [HR 15.4 (95% IC 3.6–64.7], respectively ($p < 0.001$) (Fig. 3b).

GVHD

Cumulative incidence (CI) of acute grade II–IV GVHD at day 100 was 39% (95% CI 30–48) and grade III–IV 16% (95% CI 9–24). Overall chronic GVHD at 3 years was 47% (95% CI 35–58) and moderate/severe 34% (95% CI 23–46) (Supplementary Fig. 1). Both acute and chronic GVHD were not significantly influenced by donor type, conditioning, GVHD prophylaxis neither by stem cell source. One and 3-year GRFS was 32% (95% CI 23–41) and 35% (95% CI 25–45), respectively.

Discussion

Our data confirmed that allo-SCT is a curative option for patients with R/R DLBCL, with NRM of 30% at 1 year and a 3-year EFS and OS of 38% and 44%, respectively, similar to previous studies, Supplementary Table 1. The optimal conditioning regimen before allo-SCT for DLBCL is not clearly defined. Retrospective comparisons between MAC and RIC show reduction of NRM at the expense of some increase in disease relapse but producing long-term OS rates of 25–40% comparable to MAC [4, 19]. In fact, *Glass* et al. published the results of a prospective analysis including patients with R/R T

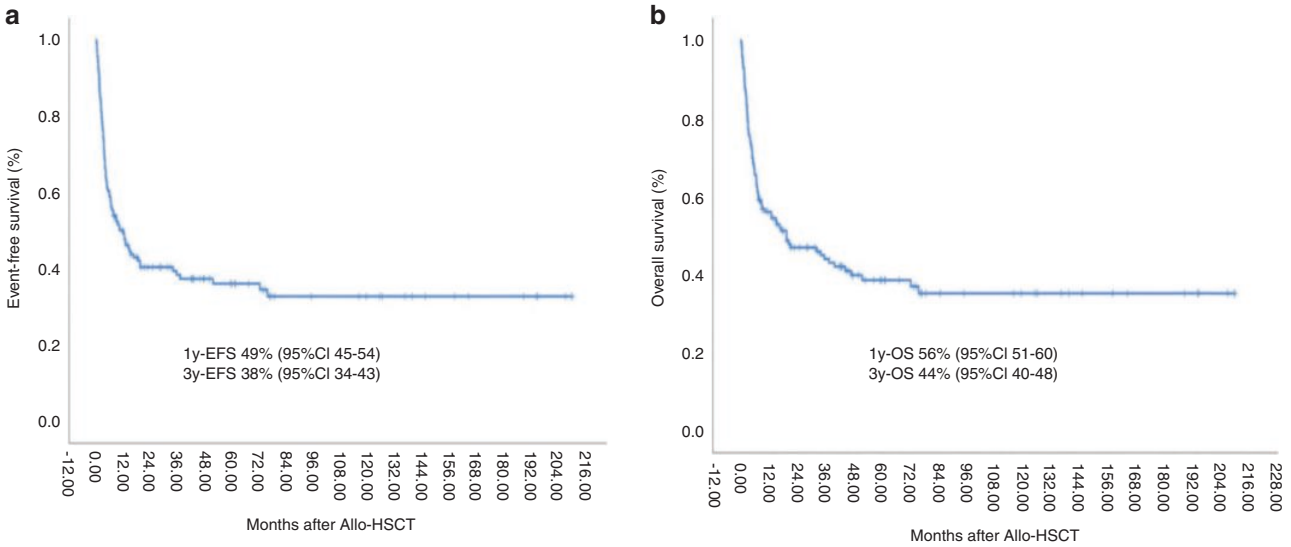

Fig. 2 Survival analysis in total cohort. EFS (**a**) and OS (**b**).

and B aggressive lymphomas who underwent allo-SCT with MAC conditioning and confirmed 3y-PFS and OS 25% and 26%, respectively [20]. Our data did not show significant differences between MAC and RIC conditioning although MAC was used in a low number of patients.

Regarding donor type, some studies have confirmed similar results in terms of survival, NRM and GVHD between matched related and unrelated donor in patients with DLBCL [21]. Recently, *Dreger* et al. showed that haploidentical allo-SCT with post-transplant Cyclophosphamide as GVHD prophylaxis was associated with a lower CI of cGVHD compared with matched sibling receiving calcineurin inhibitor based prophylaxis and unrelated donor with or without T-cell depletion [22]. In our series, we did not show differences regarding donor type in terms of survival, NRM neither GVHD. However, these results should be taken with caution considering the heterogeneity of the number of patients in each modality, different conditioning regimens and GVHD prophylaxis used.

Around 30–40% of DLBCL ASCT recipients will experience relapse or progression and, because of GVL effect in DLBCL [23, 24], such patients are often considered for allo-SCT [25]. Regarding disease status at allo-SCT, our data confirmed similar outcome in those patients with PR and CR that could be explained by the GVL effect. For patients transplanted with refractory disease other strategies are needed.

Allo-SCT in elderly patients and/or patients with comorbidities is characterized by a higher NRM. RIC and non-myeloablative conditionings have radically changed the eligible criteria of patients with DLBCL [26]. Many of these patients are elderly and heavily pretreated with multiple lines of chemotherapy and frequently include an ASCT [27]. HCT-CI is the widely used measure of patient health status and resulted in an accurate risk stratification for patients treated with RIC for lymphomas and myelomas [28]. Some studies showed that HCT-CI ≥ 3 demonstrated a potential association of NRM in a cohort of NHL patients [29]. Our study confirmed a higher NRM and lower EFS and OS with HCT-CI ≥ 2.

On the other hand, with progressively older transplants recipients the age of related donors for these patients has also increased. Although matched sibling donors are considered the first choice if available, the use of older donors may be associated with greater adverse clinical outcomes after transplant [30]. Recently, some studies have compared a young mismatched haploidentical donor with an older fully matched sibling or unrelated donor confirming similar survival but less cGVHD [31]. Conversely, another study including only patients with acute leukemia was not able to confirm an effect of donor age [32]. Our study suggests for the first time in a DLBCL population that patients receiving transplant from donors younger than 37 years have a better outcome with a longer EFS and OS.

Recent approval of CART therapy for patients with R/R DLBCL after at least two lines of therapy has established a possible curative option for these patients [6, 7]. Based on safety and lower morbimortality as compared with allo-SCT strategy, CART therapy is emerging as preferred therapy for this poor prognosis population and the question of whether there is still a role for allo-SCT in the treatment of R/R DLBCL is open [8]. Current data suggest that CART cells are preferred now over allo-SCT as first choice cellular therapy in many clinical situations. In contrast, employing allo-SCT instead of CART cells as first choice should be presently restricted to situations where CART therapy

Table 4 Univariate analysis.

	3y-EFS	*p*	3y-OS	*p*
Recipient age at allo-SCT (years)				
0–37	59% (43–74)	**0.004**	61% (45–77)	**0.009**
>37	43% (33–53)		37% (27–47)	
Interval diagnosis-allo-SCT (months)				
0–26	57% (44–69)	0.48	48% (36–60)	0.27
>26	41% (30–53)		40% (27–52)	
Period of transplant				
1995–2006	30% (15–46)	**0.005**	33% (17–49)	**0.022**
2006–2015	32% (21–43)		40% (29–52)	
2015–2018	60% (43–78)		64% (47–81)	
Donor type				
Sibling donor	35% (24–46)	0.68	43% (31–55)	0.63
Matched unrelated	39% (18–60)		43% (22–64)	
Mismatched unrelated	67% (29–100)		67% (29–100)	
Haploidentical	45% (25–65)		49% (30–69)	
Cord blood/Haplo-cord	30% (2–58)		30% (2–58)	
Number of lines prior to allo-SCT				
1–3	35% (25–45)	0.76	41% (30–51)	0.91
>3	42% (27–57)		48% (33–63)	
Previous ASCT				
Yes	36% (26–46)	0.43	42% (32–52)	0.33
No	45% (28–62)		50% (32–67)	
HCT-CI				
0–1	55% (41–68)	**0.001**	62% (48–75)	**0.001**
2	27% (11–43)		30% (14–46)	
≥3	25% (1–48)		27% (4–50)	
Disease status at allo-SCT				
CR	45% (33–56)	**0.001**	50% (38–62)	**0.001**
PR	39% (24–54)		45% (29–61)	
Active disease	12% (0–27)		12% (0–27)	
Conditioning type				
MAC	41% (23–59)	0.76	44% (26–63)	0.66
RIC	38% (28–47)		44% (34–54)	
GVHD prophylaxis				
Cyclosporine-Methotrexate	35% (20–50)	0.24	47% (31–62)	0.14
Cyclosporine-MMF	38% (20–56)		41% (23–60)	
Tacrolimus-Sirolimus	37% (17–58)		41% (21–62)	
Post-transplant Cy	49% (28–71)		54% (33–71)	
Timoglobulin based prophylaxis	35% (13–58)		35% (13–58)	
Others	0%		0%	
Stem cell source				
Peripheral blood	38% (29–47)	0.093	45% (35–54)	**0.036**
Bone marrow	50% (15–85)		50% (15–85)	
Cord blood	37% (4–71)		38% (4–71)	
Peripheral blood + Cord blood	0%		0%	
Median donor age (years)				
0–37	56% (42–70)	**0.001**	61% (47–75)	**0.001**
>37	22% (12–32)		28% (17–39)	

Table 4 (continued)

	3y-EFS	*p*	3y-OS	*p*
Donor sex				
Male	32% (21–43)	0.052	37% (27–48)	**0.04**
Female	48% (34–62)		53% (39–67)	
CMV status				
R+/D+	33% (21–46)	0.33	40% (27–53)	0.35
R+/D−	47% (32–63)		50% (35–66)	
R−/D+	44% (19–68)		56% (32–81)	
R−/D−	37% (11–62)		37% (11–62)	
Response rate on day 100				
CR	55% (44–66)	**<0.001**	58% (49–70)	**<0.001**
PR	40% (0–83)		60% (17–100)	
Active disease	0%		11% (0-26)	
Acute GVHD on day 100				
No	41% (29–54)	**<0.001**	47% (34–59)	**<0.001**
1–2	52% (38–67)		61% (46–75)	
3–4	4% (0–13)		4% (0–13)	
Chronic GVHD at 3 years				
No	35% (25–45)	**<0.001**	38% (28–48)	**0.002**
Mild	100%		100%	
Moderate	72% (38–89)		68% (45–95)	
Severe	11% (0–22)		42% (12–65)	

Bold values indicate statistical significance.

CR Complete response, *PR* Partial response, *MAC* Myeloablative, *RIC* Reduced intensity conditioning, *MMF* Mofetil mycophenolate, *CMV* Cytomegalovirus.

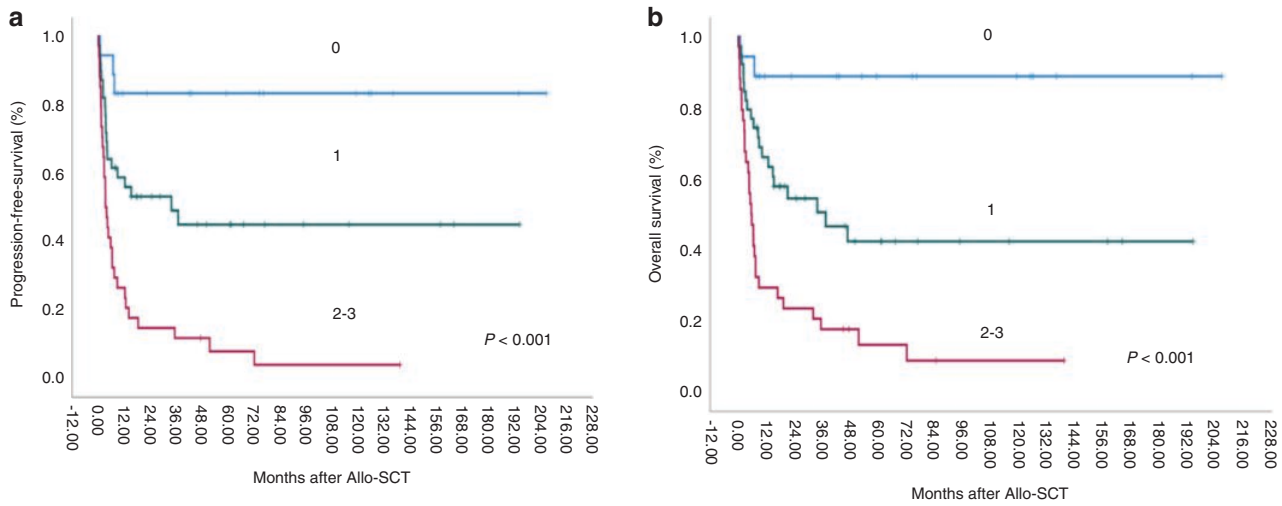

Fig. 3 Survival analysis depending on prognostic score. EFS (**a**) and OS (**b**).

deems not feasible or useful, such as patients with refractory cytopenia or incipient myelodysplastic syndrome.

However, according to the data we have now, less than half of the patients will be free of lymphoma resulting in a need to know in which situations allo-SCT could be a better option [33]. Regarding our data and based on the prognostic score we performed, R/R DLBCL patients underwent allo-SCT with 0 risk factors had 1y-EFS and 1y-OS of 83% and 89%, respectively. Comparing the results of this favorable group underwent allo-SCT with reported data in CART

trials, in which patients included had ECOG 0-1 and the majority of them had received ≥2 previous lines, both for Axicabtagene ciloleucel [7] and Tisagenlecleucel [6], higher 1y-EFS and 1y-OS were showed (89% and 83% versus 44%/35% and 59%/49%, respectively). Therefore, R/R DLBCL patients with chemosensitive disease, HCT-CI < 2 and donor age <37 years could still consider for allo-SCT versus CART as a first choice. However, one of the limitations of our prognostic score is that has been tested in a small series. Also, a validation group is needed to confirm these results. On the other hand, approval of CART therapy for patients with R/R DLBCL after at least two lines of therapy has involved that most of the patients in CAR-T cells programs belong probably to the other prognostic groups in which allo-SCT will not be likely the first choice. This score gives us approximate information which could help choosing between allo-SCT or CART cells but, in any case, randomized trials are needed to perform this comparison.

Finally, these R/R DLBCL patients should be also considered for new targeted drugs such as Polatuzumab (anti-CD79) [34], other immunotherapies such as bispecific antibodies [35] with promising results and/or clinical trials if available.

In summary, this retrospective multicenter study demonstrated that allo-SCT could be a curative option for R/R DLBCL specially in those with chemosensitive disease, HCT-CI < 2 and with a young donor. CART therapy is an attractive option for this population and both treatments should be considered individualizing the characteristic of each patient. Further prospective trials are needed to confirm these results.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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