Transplantation and Cellular Therapy 27 (2021) 614.e1–614.e8

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article
Haploidentical

Combining Three Different Pretransplantation Scores Improves Predictive Value in Patients after Haploidentical Stem Cell Transplantation with Thiotepa, Busulfan, and Fludarabine Conditioning and Post-Transplantation Cyclophosphamide

Albert Esquirol[1,*], Maria Jesus Pascual[2], Irene Garcia-Cadenas[1], Beatriz Herruzo[2], Christelle Ferrà[3], Ariadna Pérez[4], Alberto Torio[5], Anna Torrent[3], Marian Cuesta[2], Rodrigo Martino[1], Jorge Sierra[1]

[1] *Hematology Department, Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau and Jose Carreras Leukemia Research Institute, Universitat Autonoma of Barcelona, Barcelona, Spain*
[2] *Hematology Department, Hospital Regional Universitario, Malaga, Spain*
[3] *Hematology Department, Institut Català d'Oncologia Hospital Germans Trias i Pujol, Badalona, Spain and Universitat de Vic-Universitat Central de Catalunya, Catalonia, Spain*
[4] *Hematology Department, Hospital Clinico Universitario, Valencia, Spain*
[5] *Immunology Department, Hospital Regional Universitario, Malaga, Spain*

Article history:
Received 9 December 2020
Accepted 10 March 2021

Key Words:
Haploidentical transplantation with TBF conditioning
Predictive transplantation scores
Acute myelogenous leukemia

A B S T R A C T

One hundred and sixty-one patients underwent haploidentical stem cell transplantation (haploSCT) with thiotepa, busulfan, and fludarabine conditioning followed by post-transplantation cyclophosphamide (PTCy) (on days +3 and +4) and tacrolimus as graft-versus-host disease prophylaxis. Forty-two percent of patients had a high or very high revised Disease Risk Index (rDRI), 55% had an European Society for Blood and Marrow Transplantation risk score (EBMT-RS) ≥4, and 36% had an age-adjusted Hematopoietic Cell Transplant Comorbidity Index (HCT-CI-age) score ≥3. Each of these was considered an unfavorable score. Using the pretransplantation unfavorable scores that had an independent impact on each transplantation outcome studied in multivariate analysis allowed for better stratification of patient outcomes. Thus, the 3-year overall survival (OS) in patients with 0, 1, 2, and 3 unfavorable scores was 86%, 56%, 36%, and 24%, respectively. Nonrelapse mortality (NRM) was negatively impacted by the EBMT-RS and the HCT-CI-age score (3-year NRM in patients with 0, 1, and 2 unfavorable scores was 12%, 33%, and 43%, respectively), whereas the EBMT-RS and the rDRI had an impact on the 3-year relapse incidence (8%, 18%, and 41% in patients with 0, 1, and 2 unfavorable scores, respectively). In conclusion, our study shows that combining 2 or 3 of these well-defined pretransplantation scores improves the ability to predict transplantation outcomes in the setting of haploSCT with PTCy.

INTRODUCTION

Haploidentical hematopoietic stem cell transplantation (haploSCT) has become a valid alternative in patients who are candidates to receive an allogeneic SCT (alloSCT), but lack an HLA-identical donor and who urgently need an alloSCT [1-6]. The incorporation of post-transplantation cyclophosphamide (PTCy) has allowed the widespread application of haploSCT without a high incidence of primary graft failure [7], severe graft-versus-host disease (GVHD) [8], or prohibitively high nonrelapse mortality (NRM).

Initial approaches to haploSCT were published nearly 4 decades ago [7,8], proving that overcoming the HLA barrier was clinically possible [9], and since then several strategies have proven successful in adult patients. Ex vivo graft manipulation, such as megadoses of $CD34^+$ selection [10,11], $CD3^+/CD19^+$ cell depletion [12], or the Peking platform using unmanipulated grafts [13,14], led to good engraftment, but these protocols were not widely applicable outside the centers that developed them.

A significant advance in the haploSCT setting has been the introduction of high-dose cyclophosphamide after T cell-replete stem cell infusion [15]. Luznik et al. [16] published the first experience with nonmyeloablative conditioning, bone

Financial disclosure: See Acknowledgments on page 614.e4.
*Correspondence and reprint requests: Albert Esquirol, Hematology Department, Hospital de la Santa Creu i Sant Pau, Mas Casanovas 90, 08041 Barcelona, Spain.
E-mail address: aesquirol@santpau.cat (A. Esquirol).

https://doi.org/10.1016/j.jtct.2021.03.021
2666-6367/

marrow (BM) stem cell infusion, and GVHD prophylaxis based on high-dose cyclophosphamide (50 mg/kg/day) on days +3 and +4, followed by tacrolimus and mycophenolate mofetil (MMF). The first results showed 12% graft failure and a low incidence of grade III-IV acute GVHD (6%). However, a high incidence of relapse (51% and 58% at 1-year and 2-year follow-up) was reported.

In parallel to the publication by the Genova group of a T cell-replete haploSCT platform using thiotepa, fludarabine, and busulfan (TBF) as myeloablative conditioning with bone marrow transplantation followed by PTCy (on days +3 and +5), cyclosporine, and MMF as GVHD prophylaxis [17,18], we developed a haploSCT protocol based on TBF conditioning, PTCy on days +3 and +4, and single-agent tacrolimus started on day +5 as GVHD prophylaxis, as described previously [19].

In the present study, we describe the outcomes of this haploSCT protocol with a median 3-year follow-up in survivors, with the primary objective of exploring the predictive potential of 3 well-known risk scores in this specific transplantation scenario: the age-adjusted Hematopoietic Stem Cell Transplantation Comorbidity Index (HCT-CI-age), [20], the refined Disease Risk Index (rDRI) [21], and the European Society for Blood and marrow Transplant risk score (EBMT-RS) [22]. As a secondary objective, an exploratory subanalysis of the outcomes in patients with acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) was done.

METHODS

The study is a retrospective analysis of all consecutive haploSCT recipients in 4 Spanish centers using an identical protocol between June 2013 and December 2019. One hundred and sixty-one patients were included; a subset of these patients was included in a previous study analyzing feasibility and short-term results [19]. All patients provided signed informed consent for inclusion in this haploSCT protocol. Each transplantation was performed according to approved institutional protocols. The haploidentical donor and the stem cell source were selected by each transplant center.

Conditioning Regimen, Stem Cell Source, and GVHD Prophylaxis

The conditioning regimen included thiotepa on days -7 and -6 (total dose 10 mg/kg), fludarabine on days -5, -4, and -3 (total dose 150 mg/m^2), and oral busulfan on days -5, -4, and -3 (1 mg/kg/6 hours or the equivalent i.v. dose given as a single daily dose of 3.2 mg/kg). Dose adjustments were made based on pharmacokinetic monitoring. In patients age >55 years or who had undergone previous transplantation, busulfan was given for 2 days only.

In recipients of peripheral blood stem cell grafts, the target dose of CD34$^+$ cells for infusion was 5×10^6/kg of recipient weight. The target dose of total nucleated cells (TNC)/kg in bone marrow (BM) transplant recipients was 3×10^8/kg of recipient weight.

GVHD prophylaxis consisted of high-dose PTCy (50 mg/kg) i.v. on days +3 and +4 (with i.v. MESNA administered for hemorrhagic cystitis prophylaxis at a dose of 10 mg/kg/6 hours on days +3 and +4), followed by continuous-infusion tacrolimus (0.02 mg/kg) starting on day +5. Some differences from the Genoa approach were explained in our previous report [19].

Supportive Care and Definitions

Supportive care followed standard care procedures for alloSCT recipients. Details of the supportive care as well as the definitions used in the present study can be found in the online Supplementary Material.

Transplantation Prognosis Scores

Three different transplantation prognosis scores were calculated for all patients: the HCT-CI-age [20], rDRI [21], and EBMT-RS [22]. Each patient's transplantation scores were centrally revised in the study database by the principal investigator and firts author of the study (Dr. A.E.).

Statistical Analyses

SPSS version 26 (IBM, Armonk, NY) and R studio programs (R studio, Boston, MA) were used for statistical analyses. Overall survival (OS) was defined as the time from day 0 to the date of death from any cause, and progression-free survival (PFS) was defined as the time from day 0 to disease progression or death. The Kaplan-Meier method was used for estimating the actuarial PFS and OS, and the log-rank test was used to study the univariate impact of any given variable on OS and PFS. GVHD-free relapse-free survival (GRFS) was defined as the time from day 0 to the date of death from any cause, relapse, or grade III-IV acute GVHD. The cumulative incidence estimate with competing-risk analysis was used to calculate the incidences of acute and chronic GVHD, NRM, and relapse. The competing risk for NRM was relapse, and that for relapse was NRM. Competing risks for acute and chronic GVHD were disease relapse and NRM up to 100 days after stem cell infusion for acute GVHD and until the last follow-up for chronic GVHD. Cox regression analysis was used for multivariate analysis (MVA). Variables included in the MVA were lymphoid or myeloid underlying disease, source, HCT-CI-age [20], rDRI [21], the EBMT-RS [22], conditioning regimen intensity, previous alloSCT, patient and donor sex, and female to male direction. Of note, disease status and patient age were not in the final MVA, because they are included in the rDRI, EBMT-RS, and HCT-CI-age. Because AML and MDS were the most common underlying diseases, an exploratory subanalysis of their outcomes was done with the same statistical methods.

RESULTS

Patients, Donors and Engraftment

One hundred sixty-one patients were included in the analysis; clinical patient and donor characteristics are shown in Table 1. Sixty-three patients (39%) were diagnosed with AML, and 36 patients (22%) were diagnosed with MDS. Forty-two percent of the patients had a high to very high rDRI, 88 patients (55%) had a high EBMT-RS (≥4 points), and 58 patients (36%) had a HCT-CI-age ≥3. These were considered unfavorable scores for each pretransplantation scoring system.

Five patients (3%) had a primary graft failure, and 6 more patients died before day +21 without engraftment. The final cumulative incidence of neutrophil recovery (>0.5×10^9/L) and platelet recovery (>20×10^9/L) was 93% and 90%, respectively, and the median day of engraftment was day +19 (range, day +10 to day +48) and day +26 (range, day +10 to day +156), respectively.

OS and PFS

The median duration of follow-up in survivors was 36 months (range, 1 to 80 months). The OS was 66% (95% CI, 62% to 72%) at 12 months and 52% (95% CI, 48% to 56%) at 36 months (Figure 1A). In univariate analysis (UVA), variables with a positive impact on OS included disease in complete remission (CR) at haploSCT (P = .012), no prior alloSCT (P = .014), low HCT-CI-age (≤2) (P = .012), low-intermediate rDRI (P = .002), and low (≤3) EBMT-RS (P = .001) (Figure 1B). On MVA, all 3 pretransplantation predictive scores had a statistically significant impact on 3-year OS (rDRI, low-intermediate versus high-very high: P= .04; HR, 0.61; 95% CI, 0.37 to 0.91; EBMT-RS, ≤3 versus ≥4: P= .001; HR, 0.4; 95% CI, 0.24 to 0.68; HCT-CI-age, ≤2 versus ≥3: P = .03; HR, 0.59; 95% CI, 0.36 to 0.94) (Table 2).

The OS was progressively worse according to the number of unfavorable pre-SCT predictive scores present (Figure 5A). The 4 prognostic groups of patients in terms of OS were as follows: good risk, 86 ± 7% (with no unfavorable scores); intermediate risk, 56 ± 7% (with 1 unfavorable score); poor risk, 36 ± 7% (with 2 unfavorable score); and very poor risk, 24 ± 10% (with 3 unfavorable scores).

The PFS was 60% (95% CI, 56% to 64%) at 12 months and 49% (95% CI, 45% to 53%) at 36 months. In UVA, variables with an impact on PFS included disease in CR at transplantation (P = .04), no prior alloSCT (P = .003), and all 3 pre-SCT predictive scores (HCT-CI-age ≤2, P = .02; rDRI low-intermediate, P = .003; EBMT-RS ≤3, P = .001). On MVA, only 3 variables had an independent impact on PFS: no prior alloSCT (P= .024; HR, 0.53; 95% CI, 0.30 to 0.92), EBMT-RS ≤3 versus ≥4 (P= 0.001; HR, 0.4; 95% CI, 0.24 to 0.65), and HCT-CI-age ≤2 vs >3 (P = .03; HR, 0.6, 95% CI, 0.38 to 0.9. The rDRI had no independent impact on PFS (Table 2).

One-year GRFS was 56% (95% CI, 52% to 60%), and 3-year GRFS was 47% (95% CI, 43% to 50%).

Table 1
Patient and Donor Characteristics

Characteristic	Value
Number of cases	161
Patient characteristics	
Males/females, n (%)	90 (56)/71 (44)
Female donor to male recipient, n (%)	35 (22)
Age, yr, median (range)	54 (18-71)
Age ≥50 yr/≥60 yr, n (%)	97 (60)/54 (34)
Underlying disease, n (%)	
AML	63 (39)
MDS	36 (22)
ALL	20 (13)
CML or other MPS	8 (5)
CLL	6 (4)
Multiple myeloma	4 (3)
Non-Hodgkin lymphoma	15 (9)
Hodgkin disease	7 (4)
Biphenotypic acute leukemia	2 (1)
Response, n (%)	
Complete remission (first or second)	93 (58)
Other response	68 (42)
HLA mismatch (high-resolution), n (%)	
4 of 10	4 (2)
5 of 10	117 (73)
6 of 10	20 (12)
7 of 10	6 (4)
HLA mismatch (low-resolution), n (%)	
3 of 6	13 (8)
4 of 6	1 (1)
Poor ECOG performance status (>1), n (%)	35 (22)
HCT-CI-age, n (%)	
0-2	103 (64)
≥3	58 (36)
EBMT-RS, n (%)	
≤3	73 (45)
≥4	88 (55)
rDRI, n (%)	
Low	13 (8)
Intermediate	80 (50)
High	55 (34)
High/very high	12 (8)
Previous HSCT, n (%)	32 (20)
AlloHSCT, another donor, n (%)	22 (14)
Stem cell source, n (%)	
Peripheral blood stem cells	101 (63)
Bone marrow	60 (37)
Recipient CMV IgG seropositive, n (%)	128 (79)
Myeloablative/reduced-intensity conditioning, n (%)	59 (37)/102 (63)
$CD34^+$ cell dose infused, $\times 10^6$/kg, median (range)	4.6 (1-10)
Follow-up of survivors, mo, median (range)	36 (1-80)
Donor characteristics	
Age, yr, median (range)	38 (16-74)
Males/females, n (%)	100 (62)/61 (38)
Donor relationship with patient, n (%)	
Mother/father	23 (14)
Son/daughter	86 (54)
Brother/sister	52 (32)
Donor CMV IgG seropositive, n (%)	80 (50)

ALL indicates acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; NPS, neoplasm myeloproliferative syndrome; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; HSCT, hematopoietic stem cell transplantation; CMV, cytomegalovirus.

NRM and Disease Relapse or Progression

The cumulative incidence of NRM was 18% (95% CI, 12% to 24%) at 100 days, 24% (95% CI, 18% to 30%) at 1 year, and 28% (95% CI, 21% to 35%) at 3 years. The main primary cause of NRM was an opportunistic infection (60%; 27 patients).

In UVA, patient age <50 years (P = .03), HCT-CI-age ≤2 (P = .03), and EBMT-RS ≤3 (P = .006) showed a positive impact. In MVA, only 2 variables had an independent impact on NRM: EBMT-RS ≤3 versus ≥4 (P= .008; HR, 0.42, 95% CI, 0.21 to 0.79) and HCT-CI-age ≤2 versus ≥3 (P= .024; HR, 0.5; 95% CI, 0.27 to 0.91) (Table 2). The NRM increased according to the patients' pre-haploSCT HCT-CI-age and EBMT-RS (Figure 5B). Defining 3 different groups of NRM risk: good risk, 12 ± 9% (with no unfavorable scores); intermediate risk, 33 ± 11% (with 1 unfavorable score); and poor risk, 43 ± 17% (with 2 unfavorable scores).

The incidence of relapse was 15% (95% CI, 9% to 19%) at 1 year and 22% (95% CI, 14% to 28%) at 3 years (Figure 2). Only 3 patients relapsed later than 2 years after transplantation. In UVA, no prior alloSCT (P = .01), EBMT-RS ≤3 (P = .02), and rDRI low-intermediate (P = .005) had a positive impact. In MVA, 3 variables had an impact on NRM: rDRI low-intermediate versus high-very high (P= .02; HR, 0.42, 95% CI, 0.2 to 0.8), EBMT-RS ≤3 versus ≥4 (P= .016; HR, 0.38; 95% CI, 0.2 to 0.8), and prior alloSCT, no versus yes (P = .04; HR, 0.42; 95% CI, 0.19 to 0.9) (Table 2).

The relapse rate increased according to the patients' pre-haploSCT rDRI and EBMT-RS (Figure 5C). Likewise, 3 different prognostic groups were defined, good risk (8 ± 8%), intermediate risk (18 ± 11%), and poor risk (41 ± 15%), according to the number of unfavorable scores (0, 1, and 2, respectively).

Acute and Chronic GVHD

The incidence of grade II-IV acute GVHD at 100 days was 20% (95% CI, 14% to 26%), and that of grade III-IV acute GVHD was 11% (95% CI, 5% to 15%) (Figure 3A and B). Five patients died as a consequence of acute refractory GVHD; only 1 patient developed acute GVHD after day +100.

The incidences of limited, moderate, and severe chronic GVHD were 11% (95% CI, 6% to 16%), 7% (95% CI, 3% to 11%), and 6% (95% CI, 3% to 9%), respectively (Figure 4). Three patients died as a consequence of severe chronic GVHD.

Subanalysis of Patients with AML and MDS

Ninety-nine patients were included in the subanalysis, with a median age of 58 years (range, 18 to 71 years); 60% and 86% of AML and MDS age >50 years (P = .006). Patient and donor characteristics for patients with AML and MDS are provided in Supplementary Table S1.

Due to the small sample sizes, factors influencing transplantation outcomes were analyzed only by UVA. The OS at 36 months was 57% (95% CI, 52% to 62%), with no significant difference between patients with AML (58%; 95% CI, 51% to 65%) and patients with MDS (49%; 95% CI, 40% to 58%) (P = .33). PFS at 36 months was 51% (95% CI, 46% to 56%), again without a significant difference between AML (52%; 95% CI, 45% to 59%) and MDS (48%; 95% CI, 39% to 57%) (P = .6).

UVA of OS and PFS showed a positive impact of being in CR (first and second CR versus others), no prior alloSCT, rDRI low-intermediate versus high-very high, EBMT-RS ≤3 versus ≥4, and HCT-CI-age ≤2 versus ≥3 (Supplementary Table S2).

The cumulative incidence of NRM was 12% (95% CI, 6% to 18%) at 100 days and 26% (95% CI, 16% to 34%) at 36 months. The cumulative incidence of relapse at 36 months was 20% (95% CI, 12% to 28%), including 25% (95% CI, 14% to 36%) in

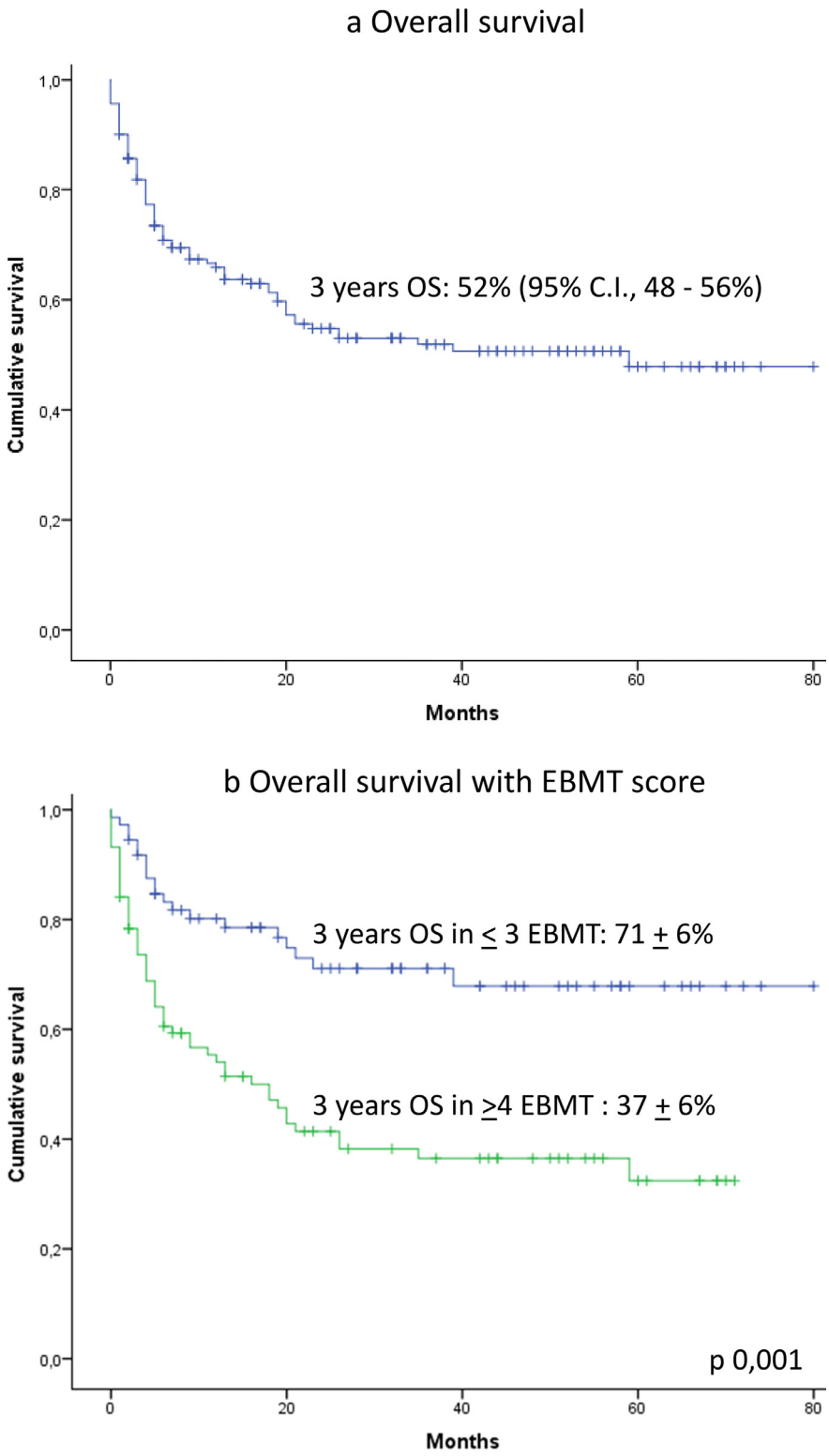


Figure 1. (A) OS. (B) OS with EBMT-RS.

patients with AML and 12% (95% CI, 2% to 22%) in patients with MDS (P = .15). In UVA, patient age <50 years, HCT-CI-age ≤2, and EBMT-RS ≤3 showed a positive impact on NRM, whereas first transplantation, EBMT-RS ≤3, and low-intermediate rDRI had a positive impact on the risk of relapse (Supplementary Table S2). The main causes of NRM were infection in 10 patients; 1 patient died as a consequence of acute refractory GVHD, and 2 patients died from chronic GVHD.

The cumulative incidences of grade II-IV and grade III-IV acute GVHD at 100 days were 20% (95% CI, 12% to 28%) and 11% (95% CI, 5% to 17%), respectively. The cumulative incidences of limited, moderate, and severe chronic GVHD were 11%

Table 2
UVA (Log-Rank Test) and MVA (COX Regression) Results

	OS				PFS				NRM				Relapse			
	UVA		MVA		UVA		MVA		UVA		MVA		UVA		MVA	
	Probability, % (95% CI)	*P* Value	HR (95% CI)	*P* Value	Probability, % (95% CI)	*P* Value	HR (95% CI)	*P* Value	CumInc (95% CI)	*P* Value	HR (95% CI)	*P* Value	CumInc (95% CI)	*P* Value	HR (95% CI)	*P* Value
rDRI																
Low-intermediate (ref)	64 (59-69)	.002	0.61 (0.37-0.91)	.04	59 (53-65)	.003	NA	.45	28 (18-38)	.56	NA	.58	15 (8-22)	.005	0.42 (0.2-0,8)	.02
High-very high	37 (31-43)				36 (30-42)				29 (18-40)				34 (23-45)			
EBMT-RS																
≤3 (ref)	71 (65-77)	.001	0.41 (0.24-0.68)	.001	67 (61-73)	.001	0.4 (0.24-0.65)	.001	19 (10-28)	.006	0.4 (0.2-0.8)	.008	15 (8-22)	.02	0.38 (0.2-0.8)	.016
≥4	37 (31-43)				34 (29-39)				36 (26-46)				30 (21-39)			
HCT-CI-age																
≤2 (ref)	58 (53-63)	.01	0.59 (0.36-0.94)	.03	55 (50-60)	.02	0.6 (0.38-0.9)	.03	23 (15-31)	.03	0.5 (0.3-0.9)	.024	22 (14-30)	.61	NA	.25
≥3	41 (34-48)				39 (32-46)				39 (27-51)				24 (13-35)			
Previous alloSCT																
No (ref)	55 (50-60)	.013	NA	.19	52 (47-57)	.003	0.53 (0.30-0.92)	.024	28 (21-35)	.52	NA	.8	21 (15-27)	.01	0.43 (0.2-0.9)	.04
Yes	32 (22-42)				31 (21-41)				31 (12-50)				37 (27-47)			

Variables included in the MVA: myeloid versus lymphoid, source, HCT-CI-age, EBMT-RS, rDRI, conditioning regimen intensity, previous alloSCT, donor sex, and related donor.

Figure 2. Relapse.

Figure 3. (A) Acute grade II-IV GVHD. (**B**) Acute grade III-IV GVHD.

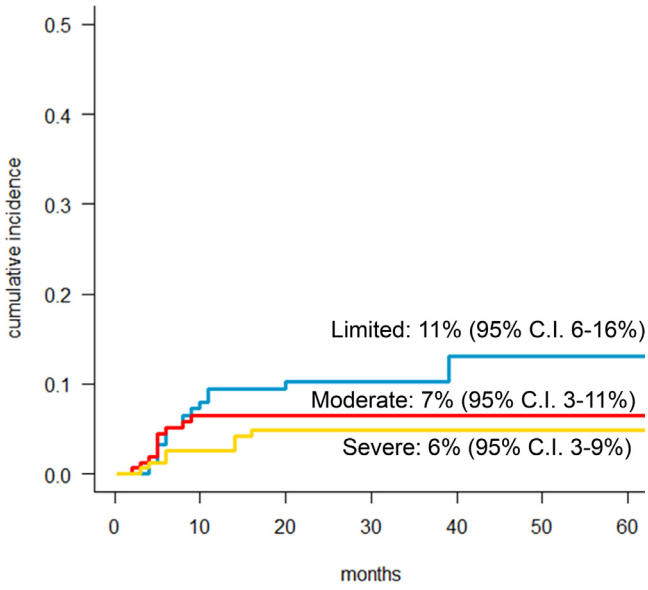
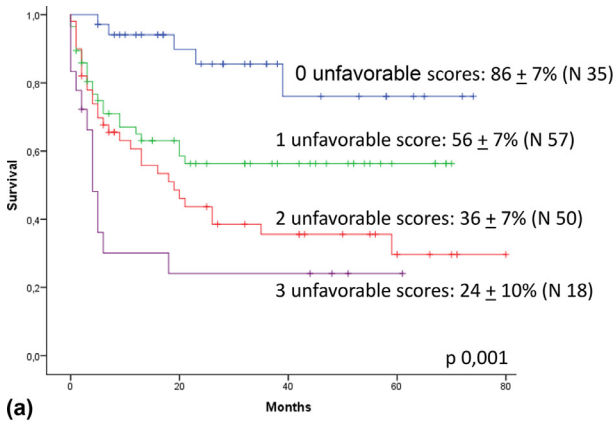
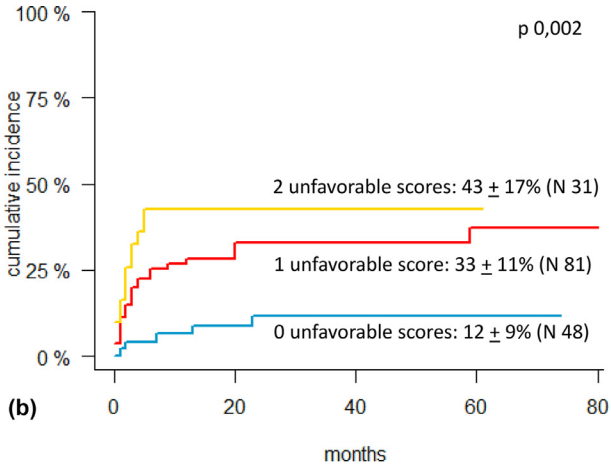


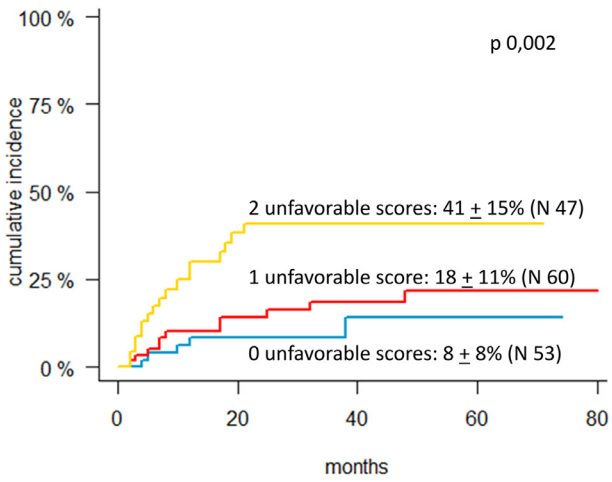
Figure 4. Chronic GVHD.



Favorable scores: ≥4 EBMT, high or very high rDRI and ≥3 HCT-CI-age



Favorable scores: ≥4 EBMT and ≥3 HCT-CI-age



(c) Favorable scores: ≥4 EBMT and high-very high rDRI

Figure 5. (**A**) OS according to unfavorable scores. (**B**) NRM according to unfavorable scores. (**C**) Relapse according to unfavorable scores.

(95% CI, 2% to 20%), 9% (95% CI, 4% to 14%), and 7% (95% CI, 3% to 11%), respectively.

DISCUSSION

After the introduction of PTCy, haploSCT has emerged as a valid option for adult patients who lack an eligible HLA-identical donor. Since the first experience with PTCy as GVHD prophylaxis published by Luznik et al. [16], the number of haploSCTs has rapidly increased in Europe and the United States [23,24], with comparable survival outcomes in haploidentical, HLA-matched related and unrelated donor transplantations [6,25].

In the present study, we analyzed the long-term follow-up (3 years) data in 161 haploSCT recipients conditioned with TBF (previously used in umbilical cord blood transplantation by the Spanish transplant group [26]) followed by PTCy (days +3 and +4) and tacrolimus (starting at day +5) as GVHD prophylaxis. Similar results in terms of neutrophil and platelet engraftment were found with respect to previously published BM haploSCT approaches [16,17].

Our updated results show better outcomes at 1 year than in the preliminary report [19]. The OS at 3-year follow-up was 52%, and we found a positive independent impact on OS of EBMT-RS $\leq$3, rDRI low-intermediate, and HCT-CI-age $\leq$2. Four risk groups were identified in terms of OS depending on the number of pretransplantation unfavorable scores, with 3-year OS of 86% (good risk, no unfavorable scores), 56% (intermediate risk, 1 unfavorable score), 36% (poor risk, with 2 unfavorable scores), and 24% (very poor risk, with 3 unfavorable scores). The PFS was 49%, with positive impacts of low EBMT-RS ($\leq$3), low HCI-CI-age ($\leq$2), and no previous alloSCT.

The 3-year cumulative incidences of NRM and relapse were 28% and 22%, respectively, and EBMT-RS $\geq$4 had an impact on both outcomes, whereas an unfavorable HCT-CI-age score ($\geq$3) had a negative impact on NRM, and an unfavorable rDRI had an impact on relapse. Combining these pretransplantation risk scores, 3 groups were identified in terms of 3-year NRM (12%, 33%, and 43%) and relapse (8%, 18%, and 41%), with increasing incidence with an increasing number of unfavorable pretransplantation scores (0, 1, or 2 unfavorable scores, respectively)

In the same line, in a large series of 502 adult patients with leukemia after unmanipulated haploSCT, higher EBMT-RS was associated with decreased OS and increased NRM and relapse [27].

In the present study, HCT-CI-age $\geq$3 was an independent predictor of NRM, OS, and PFS. The EBMT-RS and the HCT-CI combination was studied in 322 consecutive leukemia patients undergoing unmanipulated haploSCT, and the results suggested that the combination of the 2 predictive scores could better stratify the outcome of haploSCT recipients. Worse OS and higher NRM were found in patients with both EBMT-RS $\geq$4 and HCT-CI $\geq$3 [28]. Likewise, the impact of HCT-CI $\geq$3 was studied in 41 patients with Hodgkin disease who underwent haploSCT with PTCy, and a worse OS was correlated with HCT-CI $\geq$3 [29].

On the other hand, in our series, the rDRI impacted OS by predicting the risk of relapse after haploSCT. The rDRI is indeed intended to predict post-SCT outcomes linked to the risk of disease progression or relapse, but not to the risk of NRM (which is the role of the HCT-CI). In a large study of 2350 patients who underwent umbilical cord blood transplantation the rDRI was also found to predict survival by its impact on relapse and not on NRM [30]. Similar results have been found by others in the haploSCT setting, with worse OS, PFS, and relapse reported in patients with high and very high DRI in 64 consecutive haploSCTs with PTCy [31]. In a large series of 475 consecutive patients, recipients of unmanipulated haploSCT (n = 116) were compared with recipients of transplantation with matched unrelated donor (n = 178) and related identical donor (n = 181), and a high and very high DRI predicted for higher relapse and, consequently, worse OS and PFS in all 3 transplantation types [32]. In the same line, rDRI was an independent factor associated with 3 years of survival and relapse in the large series (372 patients) who underwent nonmyeloablative haploSCT with PTCy [33].

Low incidences of grade II-IV and grade III-IV acute GVHD at 100 days were found (20% and 11%, respectively), and the cumulative incidence of limited, moderate, and severe chronic GVHD were 10%, 6% and 5%, respectively, also with a low incidence of death due to GVHD. These rates of GVHD are similar to the previous experience in haploSCT with TBF conditioning by the Genova group [18] and other groups with different haploSCT platforms.

A subanalysis of patients with AML and MDS (n = 99) showed good results, similar to a those in recent study from 2 centers that also used TBF conditioning followed by PTCy in 100 patients with AML and found a 52% rate of PFS, a 56% rate of OS, and a 42% rate of GRFS, along with a 28% rate of NRM and a 21% rate of relapse [34]. Another study from Spain reported 64 patients with AML and MDS who received a myeloablative conditioning regimen based on fludarabine and busulfan followed by PTCy (on days +3 and +4) and a calcineurin inhibitor (cyclosporine or tacrolimus) plus MMF as GVHD prophylaxis. In this study, OS was 54%, NRM was 19%, and the relapse rate was 25% at a 2-year follow-up [35].

The Acute Leukemia Working Party of the EBMT analyzed a large series of haploSCT recipients with AML age >45 years. Fifty-four percent of myeloablative conditioning (MAC) and 35% of reduced-intensity conditioning (RIC) regimens were based on the TBF platform. OS was 48% for MAC recipients and 44% for RIC recipients, and PFS was 43% and 41%, respectively. The cumulative incidence of NRM was 31% for MAC recipients and 30% for RIC recipients, and the cumulative incidence of relapse was 25% and 29%, respectively, showing no significant differences based on intensity of conditioning regimen [36]. A series of 143 patients with AML conditioned with fludarabine, melphalan, and total body irradiation followed by PTCy (on days +3 and +4) and tacrolimus and MMF as GVHD prophylaxis showed a PFS and OS of 41% and 47%, respectively, at a 2-year follow-up. The cumulative incidences of relapse and NRM were 46% and 35%, respectively, in patients with active disease, and 41% and 37% in patients in CR [37].

In conclusion, our study confirms acceptable results in terms of survival, relapse, and NRM after haploSCT with TBF and PTCy in all patients and in those with AML/MDS. Most importantly, the applicability of all 3 widely used pretransplantation predictive scores in our haploSCT cohort supports their use in clinical practice for improving patient selection and guidance. Very good outcomes were found in patients with all 3 favorable scores pretransplantation (EBMT-RS, rDRI, and HCT-CI-age) (n = 35; 22%), and, conversely, very poor survival was found in those with all 3 unfavorable scores (n = 19; 12%). More studies are needed for those in between these extreme risk categories, who in fact represented the majority of transplantation recipients in this series (n = 107; 66%).

ACKNOWLEDGMENTS

Financial disclosure: This project was funded by La Marató de TV3 Foundation (file no. 20133230); AGAUR 2017 SGR 1395 from the Catalan Government; a grant from "Obra Social La Caixa," Barcelona; PERIS SLT002/16/0043 from the Catalan Government; FIS

PI17/01246 and Tercel RD16/0011/0028 from the Instituto de Salud Carlos III, Ministerio de Economía y Competitividad.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: A.E. designed the study, performed research, analyzed data, and wrote the manuscript; R.M. and J.S. designed the study and performed research; I.G.C., B.H., C.F., A.P. Al.T., An.T., and M.C. contributed essential data; and all authors approved the final version of the manuscript. R.M. and J.S. contributed equally to this work and should be considered co-first authors. A.E. and M.J.P. contributed equally to this work.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2021.03.021.

REFERENCES

1. Alshemmari S, Ameen R, Gaziev J. Haploidentical hematopoietic stem-cell transplantation in adults. *Bone Marrow Res*. 2011;2011: 303487.
2. Raiola AM, Dominietto A, di Grazia C, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. *Biol Blood Marrow Transplant*. 2014;20:1573–1579.
3. Di Stasi A, Milton DR, Poon LM, et al. Similar transplantation outcomes for acute myeloid leukemia and myelodysplastic syndrome patients with haploidentical versus 10/10 human leukocyte antigen-matched unrelated and related donors. *Biol Blood Marrow Transplant*. 2014;20:1975–1981.
4. Ciurea SO, Zhang MJ, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood*. 2015;126:1033–1040.
5. Wang Y, Liu QF, Xu LP, et al. Haploidentical vs identical-sibling transplant for AML in remission: a multicenter, prospective study. *Blood*. 2015;125:3956–3962.
6. McCurdy S, Fuchs EJ. Comparable outcomes for hematologic malignancies after HLA-haploidentical transplantation with post-transplantation cyclophosphamide and HLA-matched transplantation. *Adv Hematol*. 2015;2015: 431923.
7. Powles RL, Kay HEM, Clink HM, et al. Mismatched family donors for bone-marrow transplantation as treatment for acute leukemia. *Lancet*. 1983;321:612–615.
8. Beatty PG, Clift RA, Mickelson EM, et al. Marrow transplantation from related donors other than HLA-identical siblings. *N Engl J Med*. 1985;313:765–771.
9. Chang YJ, Huang XJ. Haploidentical SCT: the mechanisms underlying the crossing of HLA barriers. *Bone Marrow Transplant*. 2014;49:873–879.
10. Aversa F, Tabilio A, Terenzi A, et al. Successful engraftment of T cell-depleted haploidentical "three-loci" incompatible transplants in leukemia patients by addition of recombinant human granulocyte colony-stimulating factor-mobilized peripheral blood progenitor cells to bone marrow inoculum. *Blood*. 1994;84:3948–3955.
11. Aversa F, Tabilio A, Velardi A, et al. Treatment of high-risk acute leukemia with T-cell-depleted stem cells from related donors with one fully mismatched HLA haplotype. *N Engl J Med*. 1998;339:1186–1193.
12. Federmann B, Bornhauser M, Meisner C, et al. Haploidentical allogeneic hematopoietic cell transplantation in adults using CD3/CD19 depletion and reduced-intensity conditioning: a phase II study. *Haematologica*. 2012;97:1523–1531.
13. Huang XJ, Liu DH, Liu KY, et al. Treatment of acute leukemia with unmanipulated HLA-mismatched/haploidentical blood and bone marrow transplantation. *Biol Blood Marrow Transplant*. 2009;15:257–265.
14. Wang Y, Liu DH, Liu KY, et al. Long-term follow-up of haploidentical hematopoietic stem cell transplantation without in vitro T cell depletion for the treatment of leukemia: nine years of experience at a single center. *Cancer*. 2013;119:978–985.
15. O'Donnell PV, Luznik L, Jones RJ, et al. Nonmyeloablative bone marrow transplantation from partially HLA-mismatched related donors using post-transplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2002;8:377–386.
16. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008;14:641–650.
17. Raiola AM, Dominietto A, Ghiso A, et al. Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. *Biol Blood Marrow Transplant*. 2013;19:117–122.
18. Bacigalupo A, Dominietto A, Ghiso A, et al. Unmanipulated haploidentical bone marrow transplantation and post-transplant cyclophosphamide for hematologic malignancies following a myeloablative conditioning: an update. *Bone Marrow Transplant*. 2015;50(suppl 2):S37–S39.
19. Esquirol A, Pascual MJ, Ortiz M, et al. Single-agent GVHD prophylaxis with tacrolimus after post-transplant high-dose cyclophosphamide is a valid option for haploidentical transplantation in adults with hematological malignancies. *Bone Marrow Transplant*. 2017;52:1273–1279.
20. Sorror ML, Storb RF, Sandmaier BM, et al. Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2014;32:3249–3256.
21. Gratwohl A. The EBMT risk score. *Bone Marrow Transplant*. 2012;47:749–756.
22. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. *Blood*. 2014;123:3664–3671.
23. D'Souza A, Lee S, Zhu X, Pasquini M. Current use and trends in hematopoietic cell transplantation in the United States. *Biol Blood Marrow Transplant*. 2017;23:1417–1421.
24. Passweg JR, Baldomero H, Bader P, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. *Bone Marrow Transplant*. 2017;52:811–817.
25. McCurdy SR, Kasamon YL, Kanakry CG, et al. Comparable composite endpoints alter HLA-matched and HLA-haploidentical transplantation with post-transplantation cyclophosphamide. *Haematologica*. 2017;102:391–400.
26. Sanz J, Boluda JCH, Martín C, et al. Single-unit umbilical cord blood transplantation from unrelated donors in patients with hematological malignancy using busulfan, thiotepa, fludarabine and ATG as myeloablative conditioning regimen. *Bone Marrow Transplant*. 2012;47:1287–1293.
27. Wang HT, Chang YJ, Xu LP, et al. EBMT risk score can predict the outcome of leukaemia after unmanipulated haploidentical blood and marrow transplantation. *Bone Marrow Transplant*. 2014;49:927–933.
28. Chang YJ, Wang HT, Xu LP, et al. Combined model of the EBMT score modified model and the HCT-CI improves the stratification of high-risk patients undergoing unmanipulated haploidentical blood and marrow transplantation. *Leuk Lymphoma*. 2016;57:2133–2139.
29. Marani C, Raiola AM, Morbelli S, et al. Haploidentical transplants with post-transplant cyclophosphamide for relapsed or refractory Hodgkin lymphoma: the role of comorbidity index and pretransplant positron emission tomography. *Biol Blood Marrow Transplant*. 2018;24:2501–2508.
30. Paviglianiti A, Ruggeri A, Volt F, et al. Evaluation of a disease risk index for adult patients undergoing umbilical cord blood transplantation for haematological malignancies. *Br J Haematol*. 2017;179:790–801.
31. Solomon SR, Solh M, Morris LE, Holland HK, Bashey A. Myeloablative conditioning with PBSC grafts for T cell-replete haploidentical donor transplantation using posttransplant cyclophosphamide. *Adv Hematol*. 2016;2016: 9736564.
32. Bashey A, Zhang X, Jackson K, et al. Comparison of outcomes of hematopoietic cell transplants from T-replete haploidentical donors using post-transplantation cyclophosphamide with 10 of 10 HLA-A, -B, -C, -DRB1, and -DQB1 allele-matched unrelated donors and HLA-identical sibling donors: a multivariable analysis including Disease Risk Index. *Biol Blood Marrow Transplant*. 2016;22:125–133.
33. McCurdy SR, Kanakry JA, Showel MM, et al. Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide. *Blood*. 2015;125:3024–3031.
34. Pagliardini T, Castagna L, Harbi S, et al. Thiotepa, fludarabine, and busulfan conditioning regimen before T cell-replete haploidentical transplantation with post-transplant cyclophosphamide for acute mieloide leucemia: a bicentric experience of 100 patients. *Biol Blood Marrow Transplant*. 2019;25:1803–1809.
35. Gayoso J, Balsalobre P, Kwon M, et al. Busulfan based myeloablative conditioning regimens for haploidentical transplantation in high-risk acute leukemias and myelodysplastic syndromes. *Eur J Haematol*. 2018;101: 332–339.
36. Santoro N, Labopin M, Ciceri F, et al. Impact of conditioning intensity on outcomes of haploidentical stem cell transplantation for patients with acute myeloid leukemia 45 years of age and over. *Cancer*. 2019;125:1499–1506.
37. Srour SA, Saliba RM, Bittencourt MCB, et al. Haploidentical transplantation for acute myeloid leukemia patients with minimal/measurable residual disease at transplantation. *Am J Hematol*. 2019;94:1382–1387.