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Full Length Article
Analysis

Comparison of Outcomes after Unrelated Double-Unit Cord Blood and Haploidentical Peripheral Blood Stem Cell Transplantation in Adults with Acute Myelogenous Leukemia: A Study on Behalf of Eurocord and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Annalisa Ruggeri[1,2,*], Jacques-Emmanuel Galimard[3], Myriam Labopin[3], Hanadi Rafii[2], Didier Blaise[4], Fabio Ciceri[1], Jose-Luiz Diez-Martin[5], Jan Cornelissen[6], Patrice Chevallier[7], Fermin Sanchez-Guijo[8], Emma Nicholson[9], Luca Castagna[10], Edouard Forcade[11], Jürgen Kuball[12], Montserrat Rovira[13], Yener Koc[14], Jiri Pavlu[15], Zafar Gulbas[16], Jan Vydra[17], Frederic Baron[18], Jaime Sanz[19], Alexandros Spyridonidis[20], Bipin Savani[21], Eliane Gluckman[2,22], Arnon Nagler[23], Mohamad Mohty[3,24]

[1] *Hematology and BMT Unit, San Raffaele Scientific Institute, Milano, Italy*
[2] *Eurocord, Hôpital Saint Louis and IUH University Paris VII, Paris, France*
[3] *Hematology and Cellular Therapy Service, Hôpital Saint Antoine, AP-HP, Paris, France*
[4] *Institut Paoli Calmettes, Marseille, France*
[5] *Hematology Department, Hospital GU Gregorio Marañon, Instituto de Investigación Sanitaria Gregorio Marañon, Department of Medicine, Universidad Complutense de Madrid, Madrid, Spain*
[6] *Erasmus MC Cancer Institute, University Medical Centre, Rotterdam, the Netherlands*
[7] *Hematology Service, Hôtel Dieu, Nantes, France*
[8] *Hematology Department, University Hospital of Salamanca, USAL-IBSAL, Salamanca, Spain*
[9] *Department of Haematology, Royal Marsden Hospital, London, United Kingdom*
[10] *Humanitas Cancer Center, Rozzano, Italy*
[11] *CHU Bordeaux, Hôpital Haut-leveque, Bordeaux, France*
[12] *Department of Hematology,University Medical Centre, Utrecht, the Netherlands*
[13] *BMT Unit, Department of Hematology, Institute of Hematology & Oncology, Hospital Clinic, Institut Josep Carreras, Barcelona, Spain*
[14] *Medicana International, Istanbul, Turkey*
[15] *Department of Haematology, Hammersmith Hospital, Imperial College, London, United Kingdom*
[16] *Bone Marrow Transplantation Department, Anadolu Medical Center Hospital, Turkey*
[17] *Institute of Hematology and Blood Transfusion, Prague, Czech Republic*
[18] *Department of Hematology, CHU of Liège, Liège, Belgium*
[19] *Hospital Universitario y Politécnico La Fe, Valencia, Spain and CIBERONC, Madrid, Spain*
[20] *University Hospital of Patras, Patras, Greece*
[21] *Vanderbilt University Medical Center, Nashville, Tennessee*
[22] *Monacord, Centre Scientifique de Monaco, Monaco*
[23] *Hematology Division, Chaim Sheba Medical Center, Tel Aviv University, Ramat Gan, Israel*
[24] *INSERM, UMR 938, Paris, France*

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Unmanipulated haploidentical hematopoietic stem cell transplantation (HCT) with post-transplantation cyclophosphamide as graft-versus-host disease (GVHD) prophylaxis (haplo-PTCY) and unrelated double-unit umbilical cord blood transplantation (dUCBT) are feasible options for treating patients with high-risk acute myelogenous leukemia (AML). This study compared outcomes after dUCBT and haplo-HCT using peripheral blood stem cells (PBSCs) in adult patients with AML in complete remission (CR) who underwent transplantation in European

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*Correspondence and reprint requests: Annalisa Ruggeri, Hematology and BMT Unit, San Raffaele Scientific Institute, Via Olgettina 60, 20135, Milano, Italy.
E-mail address: annalisaruggeri80@hotmail.com (A. Ruggeri).

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Double cord blood transplantation
Post-transplantation cyclophosphamide

Society for Blood and Marrow Transplantation (EBMT)-affiliated centers. In a population of adults with de novo AML in first or second CR, we compared outcomes after dUCBT (n = 165) and after haplo-PTCY PBSC (n = 544) performed between January 2013 and December 2018. Patients receiving in vivo antithymocyte globulin, Campath, or ex vivo T cell depletion were excluded. The median follow-up was 33 months for the haplo-PTCY arm and 52 months for the dUCBT arm. No statistically significant differences were observed between the 2 arms in the rates of grade II-IV acute graft-versus-host disease (GVHD) (hazard ratio [HR], 1.31; P = .18), grade III-IV acute GVHD (HR, 1.17; P = .56), chronic GVHD (HR, .86; P = .48), relapse (HR, 1.07; P = .77), nonrelapse mortality (NRM) (HR, .94; P = .77), leukemia-free survival (LFS) (HR, .99; P = .95), or overall survival (OS) (HR, .99; P = .97). Favorable cytogenetic risk was the sole factor predictive of lower relapse incidence (RI). Younger age at transplantation was associated with lower NRM and higher LFS and OS. Both dUCBT and haplo-PTCY with PBSCs can be considered valid approaches for adult AML patients in CR. New strategies should be investigated in both settings to define the most appropriate conditioning regimen and potentially decrease RI and NRM through better immune reconstitution and optimal supportive care.

INTRODUCTION

Haploidentical donors and umbilical cord blood (UCB) are alternative sources of hematopoietic cells for patients lacking an HLA-matched sibling or an HLA-matched unrelated donor [1–3]. UCB transplantation (UCBT) has been used successfully over the last 3 decades with comparable results to transplantation with other donor sources, as reported in single-center reports and large registry studies [3]. Advances in UCBT were achieved with the optimal unit selection based on HLA matching and cell dose [4], the use of more appropriate regimens for myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) regimens [5,6], and the successful use of double-unit UCBT (dUCBT) in adults to overcome the cell dose limitation of single-unit UCBT [5].

The use of unmanipulated haploidentical grafts from peripheral blood stem cells (PBSCs) or bone marrow (BM) with post-transplantation cyclophosphamide (PTCY) as the backbone for graft-versus-host disease (GVHD) prophylaxis has contributed to reducing the historically high incidence of nonrelapse mortality (NRM; infection, rejection) and delayed the immune reconstitution observed with the use of T cell-depleted haploidentical grafts without increasing the incidence of GVHD. Several studies have reported comparable overall outcomes to matched-donor hematopoietic stem cell transplantation (HCT), resulting in a large increase in the use of haploidentical transplants with PTCY (haplo-PTCY) in recent years [2].

Determining the most appropriate donor and graft types is challenging and usually based on a center's experience and protocols. In the setting of RIC, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) conducted a randomized multicenter prospective phase III trial in the United States comparing dUCBT and haploidentical related donor HCT (haplo-HCT) with bone marrow (BM) grafts for the treatment of leukemia and lymphoma in adults and reported lower NRM after haplo-HCT [7]. More recently, Wagner et al. [8] reported comparable survival after UCBT (single or double) and haplo-HCT (with BM or PBSC grafts) after a MAC regimen, with increased NRM in UCBT with a greater degree of HLA mismatches [8].

The aim of the present study was to compare outcomes after dUCBT and haplo-HCT using PBSCs in a population of adults with acute myelogenous leukemia (AML) in complete remission (CR) who underwent transplantation at a European Society for Blood and Marrow Transplantation (EBMT)-affiliated center.

METHODS

Study Design and Definition

We analyzed all adults (age ≥18 years) with de novo AML available in the EBMT and Eurocord databases who underwent a first allogeneic HCT while in first or second CR between January 2013 and December 2018. Grafts were double-unit unrelated UCB or related haploidentical PBSCs (≥2 recipient-donor HLA mismatches). All patients undergoing haplo-HCT received PTCY as GVHD prophylaxis in combination with calcineurin inhibitors and mycophenolate mofetil, according to center policy; this is designated the Haplo-PTCY arm. Patients who received in vivo antithymocyte globulin (ATG), Campath, or ex vivo T cell depletion were excluded.

Transplantations were performed in 162 transplantation centers; 26 centers performed only UCBTs, 116 performed only Haplo-PTCYs, and 20 performed both operations. Disease stage was defined according to International Bone Marrow Transplant Registry criteria [9]. Poor-risk cytogenetics for AML included complex karyotype (>3 abnormalities [abn]), add(5q), del(5q), del (7q)/-7, t(6;9), t(6;11), t(10;11), abn(3) [10].

For patients undergoing dUCBT, HLA matching considered antigen-level typing for HLA-A and HLA-B and allele-level typing of HLA-DRB1. Then HLA disparity was calculated based on the maximal number of HLA mismatches between UCB unit 1/UCB unit 2 and the patient.

Conditioning regimen intensity was defined according to current practice [11]. EBMT centers commit to obtain informed consent according to the local regulations applicable at the time of transplantation to report pseudonymized data to the EBMT. All patients or their legal guardians provided informed consent for transplantation according to the guidelines of the Declaration of Helsinki. The Institutional Review Board of the EBMT Acute Leukemia Working Party/Eurocord approved this study.

Endpoints

The primary endpoint was leukemia-free survival (LFS), calculated from the date of transplantation until relapse or death. Patients alive and free of disease were censored at the last follow-up. Overall survival (OS) was calculated from the date of transplantation until death or last follow-up. Relapse incidence (RI) was defined as the time from transplantation until the first event of relapse. Death without relapse was a competing event. NRM was defined as death without relapse. Neutrophil recovery was defined as achievement of an absolute neutrophil count $\geq .5 \times 10^9$/L for 3 consecutive days. Death and consecutive transplantations were competing events. The diagnosis and grading of acute GVHD (aGVHD) [12] and chronic GVHD (cGVHD) [13] were performed at +the transplantation centers using standard criteria. Relapse and death were competing events for GVHD outcomes.

Statistical Analysis

Quantitative variables were recorded as median and interquartile range (IQR); categorical variables, as number and percentage. Patient-, disease-, and transplantation-related variables were compared between the dUBCT and Haplo-PTCY groups using the chi-square or Fisher exact test for categorical variables and the Wilcoxon test for quantitative variables. The probabilities of OS and LFS were calculated using the Kaplan-Meier method, and the log-rank test was used for univariate comparisons.

Neutrophil engraftment, grade II-IV aGVHD, cGVHD, RI, and NRM were calculated with the cumulative incidence (CuI) method and Gray's test for univariate comparisons [14]. The median duration of follow-up was calculated using the reverse Kaplan-Meier method. All outcomes were censored at 2.5 years owing to a shorter follow-up in the Haplo-PTCY group.

Multivariate analyses (MVAs) were performed using a Cox proportional hazards regression model for LFS and OS and a cause-specific Cox proportional hazards regression model for GVHD, NRM, and RI [15]. The final MVA models included the following variables: transplantation strategy (Haplo-PTCY or dUCBT), disease status at HCT, cytogenetic risk group, age at HCT, type of conditioning regimen (MAC versus RIC), and Karnofsky Performance Status ≥90. To test for a center effect, we introduced a random effect or frailty for each center into the model. All P values were 2-sided. Statistical analyses

Table 1
Patient and Disease Characteristics

Characteristic		Haplo-PTCY Arm (N = 544)		dUCBT Arm (N = 165)		*P* value
Follow-up (before censoring), y (95% CI)		2.5	(2.2-2.8)	4.3	(4-5)	<.001
Age, yr, median (IQR)		53	(42-62)	53	(39-61)	.67
Year of transplantation, median (IQR)		2017	(15-18)	2014	(13-16)	<.001
Time from diagnosis to transplantation, mo, median (IQR)		6.2	(4.7-14)	6.5	(4.5-16)	.58
Disease status at transplantation, n (%)						
	CR1	375	(69)	106	(64)	.26
	CR2	169	(31)	59	(36)	
Patient sex, n (%)						
	Male	295	(54)	92	(56)	.73
	Female	249	(46)	73	(44)	
KPS, n (%)						
	< 90	114	(22)	40	(28)	
	≥90	400	(78)	102	(72)	.14
	Missing	30		23		
Recipient CMV serostatus, n (%)						
	Negative	123	(23)	56	(35)	.003
	Positive	412	(77)	106	(65)	
	Missing	9		3		
Cytogenetics, n (%)						
	Good	40	(9)	12	(10)	.44
	Intermediate	314	(71)	78	(65)	
	Poor	89	(20)	30	(25)	
	Missing	101		45		
Conditioning regimen, n (%)						
	RIC	220	(40)	127	(77)	<.001
	MAC	324	(60)	38	(23)	
TBI, n (%)						
	No	438	(80)	8	(5)	<.001
	Yes	106	(20)	157	(95)	

CMV indicates cytomegalovirus.

were performed with R version 4.0.2 software packages (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient, Disease, and Transplantation Characteristics

Patient and disease characteristics are summarized in Table 1. A total of 709 adult patients with AML underwent either Haplo-PTCY (n = 544) or dUCBT (n = 165) between January 2013 and December 2018. Before censoring, the median duration of follow-up was shorter for the Haplo-PTCY group (2.5 years versus 4.3 months; $P < .001$). Haplo-PTCY transplantations were performed more recently ($P < .001$), and Haplo-PTCY recipients more often had a positive cytomegalovirus serology ($P = .003$) and were more likely to receive a MAC regimen ($P < .001$). Busulfan-based and treosulfan-based MAC were the most frequently used MAC regimens in the Haplo-PTCY group, whereas total body irradiation (TBI)-based regimens (>6 Gy) were most commonly used in the dUCBT group. RIC regimens were used more frequently in the dUCBT group compared with the Haplo-PTCY group (74% versus 16%). Details of the conditioning regimens and GVHD prophylaxis are provided in Supplementary Table S1.

For Haplo-PTCY recipients, the median cell doses were 9.4×10^8 total nucleated cells (TNCs) (IQR, 7.1 to 12.2×10^8) and 6.7×10^6 $CD34^+$ cells (IQR, 5.1 to 8.2×10^6). For dUCBT recipients, the median cell doses (UCB1 + UCB2) at cryopreservation were 4×10^7 (IQR, 3.3 to 5.1×10^7) for TNCs and 1.4×10^5 (IQR, .9 to 1.9×10^5) for $CD34^+$ cells. Recipients and dUCBT pairs had 0 to 1/6 mismatches in 26% of cases, 2/6 mismatches in 71%, and 3/6 mismatches in 3%. Graft characteristics for both treatment strategies, including cell dose, HLA matching, and sex mismatches, are described in Supplementary Table S1.

Engraftment and GVHD

The CuI of day 60 neutrophil engraftment was 95% after Haplo-PTCY and 94% after UCBT. Overall, 34 patients experienced graft failure (Haplo-PTCY, n = 25; dUCBT, n = 9). Of these, 23 died early within 90 days after HCT, 10 underwent another HCT, and 1 was alive at a follow-up of 120 days (9 patients were missing information on neutrophil engraftment). The median time to neutrophil engraftment was 19 days (IQR, 17 to 24 days) for the Haplo-PTCY group and 25 days (IQR, 19 to 32 days) for the UCBT group. The CuI of day 180 platelet engraftment was 84.8% (95% confidence interval [CI], 81.3% to 87.7%) for the Haplo-PTCY group and 82.4% (95% CI, 75.2% to 87.6%) for the UCBT group, with a median time of 16 days (range, 22 to 28 days) and 40 days (range, 32 to 49 days), respectively.

The CuI of day 100 grade II-IV aGVHD was 35% after Haplo-PTCY and 44% after dUCBT ($P = .02$), and that for grade III-IV aGVHD was 14% and 18%, respectively ($P = .23$). MVA showed no significant differences between the groups in grade II-IV aGVHD (HR, 1.31; $P = .18$) and grade III-IV aGVHD (HR, 1.17; $P = .56$). Patients in second CR had an increased risk of developing grade III-IV aGVHD (HR, 1.78; $P = .007$) (Table 3).

Table 2
Outcomes of AML after Haplo-PB and dUCBT

Outcome	Haplo-PTCY Arm				dUCBT Arm			
	N	Event (n at time t)	Estimation (95%CI)		N	Event (n at time t)	Estimation (95%CI)	
Median follow-up (yr)	544		2.5		165		2.5	
OS (2 yr)	544	178	64.2	(59.7-68.3)	165	64	59.4	(51.2-66.6)
LFS (2 yr)	544	205	59.0	(54.5-63.3)	165	70	55.9	(47.8-63.2)
PMN recovery (60 d)	535	508	95.0	(92.7-96.5)	164	154	93.9	(88.7-96.7)
aGVHD grade II/IV (100 d)	519	181	34.9	(30.8-39.0)	153	68	44.4	(36.4-52.1)
aGVHD grade II/IV (100 d)	519	73	14.1	(11.2-17.2)	153	28	18.3	(12.6-24.8)
GRFS (2 yr)	523	268	45.3	(40.7-49.7)	161	90	43.1	(35.2-50.7)
RI (2 yr)	544	88	18.0	(14.7-21.6)	165	35	22.2	(16.1-29.0)
NRM (2 yr)	544	117	22.9	(19.3-26.7)	165	35	21.9	(15.8-28.6)
cGVHD (2 yr)	518	164	35.1	(30.8-39.5)	161	50	32.3	(25.0-39.8)
cGVHD, extensive (2 yr)	512	56	12.2	(9.4-15.4)	157	13	8.8	(4.9-14.0)

PMN indicates polymorphonuclear; GRFS, Graft-versus-host disease-free/relapse-free survival.

The CuI of cGVHD at 2 years was 35% after Haplo-PTCY versus 32% after dUCBT (P = .48), and the CuI of extensive cGVHD was 12% and 9%, respectively (P = .07). Graft source was not associated with an increased risk of cGVHD in the MVA (HR, .86; P = .48) (Table 3). Table 2 summarizes the major outcomes in the 2 groups, and Table 3 reports the results of the MVA. Univariate analysis results are provided in Supplementary Table S2.

Relapse and NRM

The CuI of 2-year relapse was 18% after Haplo-PTCY and 22% after dUCBT (P = .28) (Table 2, Figure 1A). On MVA, the risk of relapse was not statistically different between the 2 treatment groups (HR, 1.07; P = .77), whereas the relapse risk was increased in patients with poor cytogenetics (HR, 1.77; P = .01) (Table 3).

The CuI of NRM at 2 years was 22.9% after Haplo-PTCY and 18.9% after dUCBT (P = .99). NRM was not different between the 2 groups (HR, .94; P = .77). NRM was higher in patients undergoing transplantation in second CR (HR; 1.55, P = .01) and in those who underwent transplantation at an older age (per 10-year increment) (HR, 1.25; P = .004) (Figure 1B, Table 3, Supplementary Table S2).

Infection and GVHD were the most common causes of transplantation-related death in both groups (infection, 8% after Haplo-PTCY and 3% after dUCBT; GVHD, 6% and 8%, respectively). Death from disease recurrence was reported in 13% of Haplo-PTCY recipients and in 18% of dUCB recipients (data not shown).

LFS and OS

The 2-year probability of LFS was 59% after Haplo-PTCY and 56% after dUCBT (P = .33) (Figure 1C). On MVA, LFS was not statistically different between the transplant types (HR, .99; P = .95). The factors independently associated with lower LFS were poor performance status (Karnofsky Performance Status <90%) (HR, 1.37; P = .03), and older age at HCT (HR, 1.12; P = .03) (Table 3).

The probability of OS at 2 years was 64% after Haplo-PTCY and 59% after dUCBT (P = .26) (Figure 1D). There was no difference in OS with respect to graft source (HR, .99; P = .97). Older age at transplantation was the sole factor associated with worse OS (HR, 1.15; P = .01).

DISCUSSION

This study of 709 patients comparing HCT outcomes from haploidentical donors using PBSCs with PTCY-based GVHD prophylaxis with dUCBT in adult patients with AML in CR shows that OS and LFS are similar for dUCBT and Haplo-PTCY, with older age at transplantation the sole factor predictive of worse survival in both groups. Moreover, no between-group difference in outcomes was observed in terms of engraftment, aGVHD, cGVHD, relapse, and NRM.

Neutrophil recovery was similar in the 2 groups despite the heterogeneity in conditioning regimens, with the majority of the patients in the Haplo-PTCY group receiving a MAC regimen (mainly busulfan-based).

Although not statistically significant, the rate of grade II-IV aGVHD was lower after Haplo-PTCY compared with dUCBT, but no differences were observed for grade III-IV aGVHD, cGVHD and extensive cGVHD. Moreover, in line with published results [8,16], the RI and NRM at 2 years were similar in the 2 groups.

When analyzing the impact of other patient- and disease-related prognostic factors, the MVA identified 3 factors that most closely predicted outcome. AML risk group was predictive of lower RI, and younger age and earlier disease remission stage were associated with lower NRM.

The development of dUCBT has enabled the provision of an adequate cell dose to patients lacking an optimal single UCB unit, and for adult patients it has extended access to UCBT. The use of non-ATG-based conditioning regimens and the improvement in UCB unit selection based on optimal doses of TNCs and $CD34^+$ cells, minimal allele-level HLA disparity, and lower ABO incompatibility also have allowed for further improvement of dUCBT outcomes [17].

In the haplo-HCT setting, PTCY proved to be highly effective in preventing GVHD in patients with AML in CR and compares favorably with standard GVHD prophylaxis in matched sibling and matched unrelated donor transplantations. Recent data from the Center for International Blood and Marrow Transplant Research demonstrated that both PTCY and haploidentical donor are associated with increased rates of viral infections [18], contributing to a high incidence of NRM and increased overall mortality [19].

Comparative studies between Haplo-PTCY and UCBT are mainly registry-based and are limited by the heterogeneity of conditioning regimens, GVHD prophylaxis, and stem cell sources for haplo-HCT. In a prospective trial, Sanz et al. [20] compared 22 patients who underwent Haplo-PTCY with BM grafts

Table 3
Multivariate Analysis for Patients with AML

Variables		HR	95% CI	*P* Value
OS	dUCBT vs Haplo PTCY	.99	(.71-1.39)	.97
	Status at transplantation: CR2 vs CR1	1.27	(.96-1.68)	.09
	Cytology: poor-risk group	1.34	(.95-1.90)	.10
	MAC vs RIC	.98	(.71-1.33)	.88
	KPS ≥90 vs <90	.79	(.59-1.07)	.13
	Age at transplantation by 10-yr increment	1.15	(1.03-1.29)	**.01**
LFS	dUCBT vs Haplo-PTCY	.99	(.72-1.35)	.95
	Status at transplantation: CR2 vs CR1	1.22	(.94-1.58)	.14
	Cytology: poor-risk group	1.30	(.93-1.80)	.12
	MAC vs RIC	.98	(.73-1.31)	.87
	KPS ≥90 vs <90	.73	(.56-.97)	**.03**
	Age at transplantation by 10-yr increment	1.15	(1.01-1.25)	**.03**
RI	dUCBT vs Haplo-PTCY	1.07	(.68-1.69)	.77
	Status at transplantation: CR2 vs CR1	.87	(.57-1.32)	.52
	Cytology: poor-risk group	1.77	(1.14-2.75)	**.01**
	MAC vs RIC	.97	(.63-1.50)	.90
	KPS ≥90 vs <90	.73	(.48-1.10)	.14
	Age at transplantation by 10-yr increment	1.00	(.86-1.16)	.99
NRM	dUCBT vs Haplo-PTCY	.94	(.61-1.45)	.77
	Status at transplantation: CR2 vs CR1	1.55	(1.10-2.18)	**.01**
	Cytology: poor-risk group	.91	(.55-1.51)	.71
	MAC vs RIC	.99	(.66-1.47)	.94
	KPS ≥90 vs <90	.74	(.51-1.08)	.12
	Age at transplantation by 10-yr increment	1.25	(1.07-1.45)	**.004**
GRFS	dUCBT vs Haplo-PTCY	.94	(.72-1.23)	.65
	Status at transplantation: CR2 vs CR1	1.26	(1.01-1.58)	**.04**
	Cytology: poor-risk group	1.25	(.94-1.66)	.12
	MAC vs RIC	1.06	(.82-1.36)	.66
	KPS ≥90 vs <90	.76	(.60-.96)	**.02**
	Age at transplantation by 10-yr increment	1.02	(.94-1.12)	.59
aGVHD grade II-IV	dUCBT vs Haplo-PTCY	1.31	(.88-1.96)	.18
	Status at transplantation: CR2 vs CR1	1.27	(.95-1.70)	.11
	Cytology: poor-risk group	1.15	(.78-1.68)	.48
	MAC vs RIC	1.01	(.71-1.43)	.96
	KPS ≥90 vs <90	.78	(.56-1.07)	.12
	Age at transplantation by 10-yr increment	1.06	(.95-1.19)	.29
aGVHD grade III-IV	dUCBT vs Haplo-PTCY	1.17	(.69-1.96)	.56
	Status at transplantation: CR2 vs CR1	1.78	(1.17-2.71)	**.007**
	Cytology: poor-risk group	1.13	(.63-2.02)	.68
	MAC vs RIC	1.26	(.77-2.05)	.36
	KPS ≥90 vs <90	.77	(.48-1.24)	.28
	Age at transplantation by 10-yr increment	.94	(.80-1.11)	.49
cGVHD	dUCBT vs Haplo-PTCY	.86	(.56-1.32)	.48
	Status at transplantation: CR2 vs CR1	1.00	(.73-1.38)	.99
	Cytology: poor-risk group	.90	(.60-1.36)	.62
	MAC vs RIC	.79	(.55-1.13)	.20
	KPS ≥90 vs <90	.99	(.70-1.41)	.96
	Age at transplantation by 10-yr increment	.95	(.84-1.07)	.37

and 23 patients with a single UCBT after a MAC regimen based on the association of busulfan, thiotepa, and fludarabine. No statistically significant between-group differences in grade II-IV aGVHD, extensive cGVHD, NRM, or RI were observed, whereas the 2-year OS was superior for the Haplo-PTCY group. Importantly in this study, single UCBT was based on the use of ATG for GVHD prophylaxis. Recent findings clearly demonstrate increased mortality and delayed immune reconstitution with the use of ATG, especially in patients with malignancies. ATG severely impacts T cell recovery after UCBT, with detrimental effects on infections, NRM, RI, and survival [21]. The use of ATG in patients receiving UCBT outside clinical trials should be handled cautiously. Individualized dosing and therapeutic drug monitoring could aid in determining the optimal ATG dosage schedule to improve outcomes. The dUCBT platform has been conceived as an ATG-free platform, which might help explain the better results in our present series.

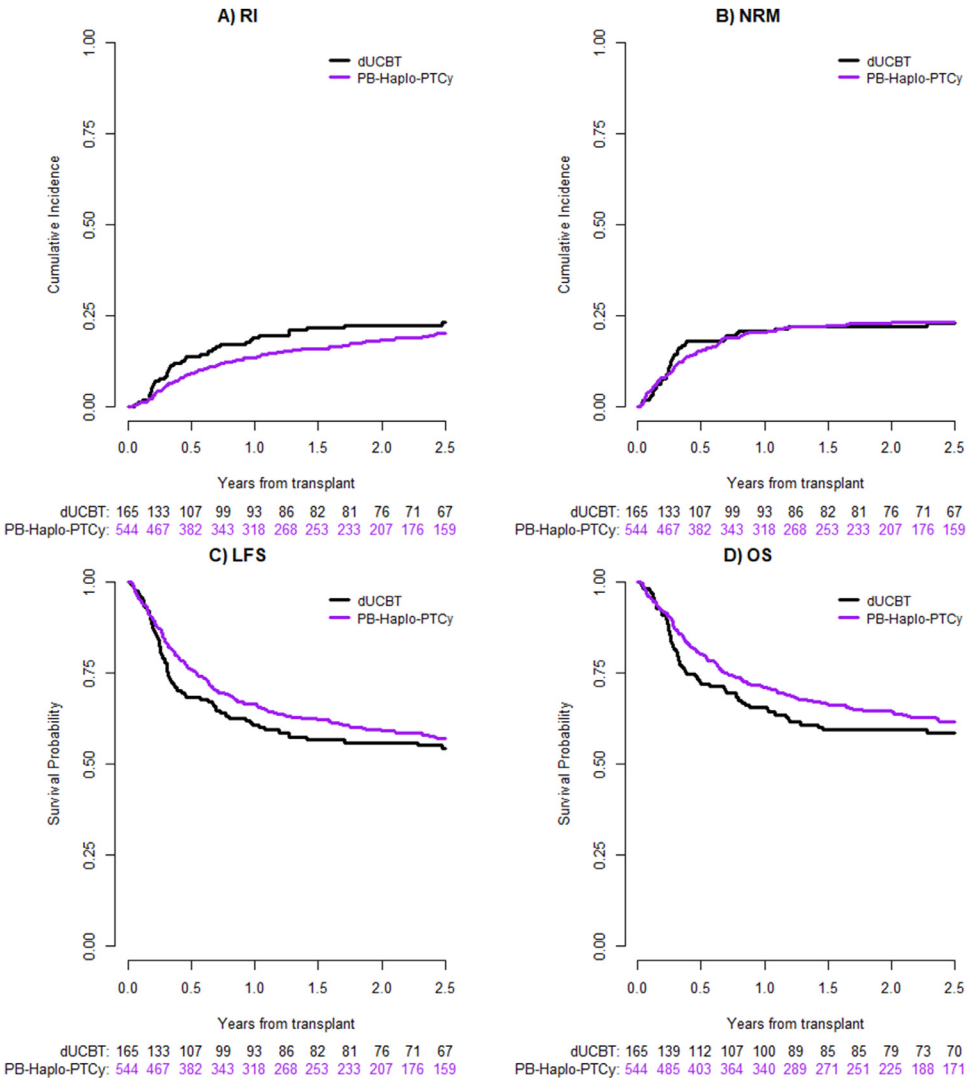

Figure 1. Outcomes after Haplo-PTCY and dUCBT. (A) RI; (B) NRM; (C) LFS.

In a recently published phase III randomized trial [7] comparing dUCBT and haplo-HCT using PTCY in 368 patients age 18 to 70 years with lymphoma or acute leukemia after a TBI-based RIC regimen, although the primary endpoint of progression-free survival was not different among the 2 groups, dUCBT was associated with higher NRM and lower OS. Patient accrual was difficult owing to the consistent increase in the use of haploidentical donors and a decline in the use of UCBT during the time period, which might have limited trial participation.

Our results confirm that use of haplo-HCT using PBSCs with PTCY is as effective as dUCBT in patients with AML in CR. Our study has several limitations owing to its retrospective registry-based design and the wide heterogeneity in patient characteristics, conditioning regimens, and GVHD prophylaxis. We are aware that in the dUCBT group, some transplantations were performed with a very low cell dose, which might have a detrimental impact on outcomes. Indeed, we aimed to report the different practices in transplantation centers, and we included all the consecutive cases reported to the registry to avoid selection bias. We believe that this is important for the transplantation community. However, despite an increase in the use of RIC and low-dose TBI-based conditioning regimens in the majority of dUCBT recipients, graft failure was not increased in this group.

In our series, patients in the Haplo-PTCY group most frequently received a MAC regimen, which should be carefully considered when interpreting our results. Several studies have suggested the possibility of using more intensive conditioning regimens in the dUCBT setting according to patient fitness and clinical course, and thus a careful comparison based on conditioning regimen is warranted.

Other limitations include the earlier year of transplantation in the dUCBT group, reflecting more recent changes in transplantation practices across centers [22]. In addition, we were unable to analyze chimerism and minimal residual disease data, major prognostic factors in patients with hematologic malignancies. Importantly, the reasons for selecting a haploidentical donor versus dUCB could not be identified, highlighting the role of a potential center effect.

Currently, the choice of an alternative donor source is driven mainly by institutional expertise, the algorithm for donor selection, and procedure-related costs. Haploidentical and dUCB grafts have the advantages of ready availability and prompt procurement for urgent transplantation needs and offer a shorter delay from indication to transplantation. Both

grafts may be used in emergency situations, as reflected in the Coronavirus disease 19 pandemic period [23]. UCB grafts offer the advantages of being off-the-shelf products, already typed and ready for immediate use. Haploidentical grafts may be preferred by transplantation centers based on lower cost of graft procurement and the availability of family donors in the post-transplantation setting. However, cost information needs to be addressed with caution in light of recent data comparing the 5-year health care burden with long-term health care requirements after transplantation with UCB, BM, or PBSC grafts [24]. In that study, recipients of UCB grafts had the lowest 5-year health care burden compared with recipients of BM and PBSC grafts. Unfortunately, recipients of haploidentical transplants were infrequent in that cohort (prior to 2016) and so were excluded.

In conclusion, with the accumulating experience and longer follow-up data, PTCY-based haploidentical donor PBSC transplantation is now considered a valid option for transplantation-eligible patients without an available HLA-matched donor. Compared with dUCBT, Haplo-PTCY using PBSCs showed similar outcomes in adult AML patients in remission. Further evaluation of conditioning regimen intensity, supportive care, and center effects will aid the identification of strategies to potentially decrease RI and NRM with better immune reconstitution [25] and fewer infectious complications [26,27] and optimize supportive care in both the UCBT and haplo-HCT settings.

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APPENDIX. THE AUTHORS THANK THE FOLLOWING PIS FROM PARTICIPATING EBMT CENTERS

Stefan Klein	Universitaetsmedizin Mannheim III, Medizinische Klinik	Germany
Olivier Hermine	Hôpital Necker, Service Hematologie Adulte	France
Michael Kiehl	Klinikum Frankfurt (Oder), Medizinische Klinik I	Germany
Jakob Passweg	University Hospital, Hematology	Switzerland
Joan Hendrik Veelken	Leiden University Hospital, BMT Centre Leiden	The Netherlands
Donald Bunjes	Klinik fuer Innere Medzin III, Universitätsklinikum Ulm	Germany
Jane Apperley	Imperial College, Department of Haematology	United Kingdom
Henrik Sengeloev	Bone Marrow Transplant Unit, National University Hospital	Denmark
Gerard Socié	Hopital St. Louis, Department of Hematology & BMT	France
Gerard Socié	Hopital St. Louis, Department of Hematology & BMT	France
Johan Maertens	University Hospital Gasthuisberg, Department of Hematology	Belgium
Yana Novis	Hospital Sirio-Libanes, Hematology and Bone Marrow Transplant Unit	Brazil
Philippe Lewalle	Institut Jules Bordet, Experimental Hematology	Belgium
Emanuele Angelucci	Ospedale San Martino, Department of Hematology II	Italy
Ben Carpenter	University College London Hospital, Department of Haematology	United Kingdom
Werner Rabitsch	Medizinische Universitaet Wien, Klinik fuer Innere Medizin I	Austria
Didier Blaise	Programme de Transplantation &Therapie Cellulaire, Centre de Recherche en Cancérologie de Marseille	France
Alessandro Busca	S.S.C.V.D Trapianto di Cellule Staminali, A.O.U Citta della Salute e della Scienza di Torino	Italy
Alessandro Busca	S.S.C.V.D Trapianto di Cellule Staminali. A.O.U Citta della Salute e della Scienza di Torino	Italy
Eric Deconinck	Hopital Jean Minjoz, Service d`Hématologie	France
Xavier Poiré	Cliniques Universitaires St. Luc, Department of Haematology	Belgium
N. Schaap	Nijmegen Medical Centre, Department of Hematology	The Netherlands
Concepcion Herrera Arroyo	Hospital Reina Sofia, Córdoba Hospital	Spain
Arancha Bermúdez Rodríguez	Hospital U. Marqués de Valdecilla, Servicio de Hematología-Hemoterapia	Spain
Andrew Clark	Bone Marrow Transplant Unit, Beatson, West of Scotland Cancer Centre	United Kingdom
Gandhi Damaj	CHU Caen, Institut d'hématologie de Basse-Normandie	France
Sébastien Maury	Hôpital Henri Mondor, Hematology Service	France
Anjum Khan	Yorkshire Blood & Marrow Transplant Programme, Haematology Department, Level 3	United Kingdom
Andy Peniket	Department of Haematology, Cancer and Haematology Centre	United Kingdom
Thomas Schroeder	University Hospital, Department of Bone Marrow Transplantation	Germany
Yves Chalandon	Département d`Oncologie, Service d`Hématologie, Hôpitaux Universitaires De Genève	Switzerland
Véronique Leblond	Universite Paris IV, Hopital la Pitié-Salpêtrière, Hematologie Clinique	France
Xavier Leleu	Hopital La Miletrie, Bone Marrow Transplant Unit	France
Francesco Onida	Fondazione IRCCS, Ca' Granda Ospedale Maggiore Policlinico IRCCS	Italy
Claude Eric Bulabois	CHU Grenoble Alpes-Université Grenoble Alpes, Service d`Hématologie	France
Jacques-Olivier Bay	CHU Estaing, Service d'hématologie clinique Adulte et pédiatrie	France
Ibrahim Yakoub-Agha	CHU de Lille, LIRIC, INSERM U995	France
Carlos Solano	Hospital Clínico de Valencia, Servicio de Hematología	Spain
Shankara Paneesha	Birmingham Heartlands Hospital, Department of Haematology	United Kingdom
Luigi Rigacci	Ospedale S. Camillo-Forlanini, Department of Hematology and BMT	Italy
Mark Ringhoffer	Klinikum Karlsruhe GmbH III, Medizinische Klinik	Germany
Giovanni Grillo	Asst Grande Ospedale Metropolitano Niguarda, Hematology Department	Italy
Gesine Bug	Goethe-Universitaet, Medizinische Klinik II, Hämatologie, Medizinische Onkologie	Germany
Marco Casini	Hospital San MaurizioDept. of Hematology - BMT Unit	Italy
Radovan Vrhovac	University Hospital Center RebroKispaticeva 12	Croatia

(*continued*)

Keith M. O. Wilson	Department of HaematologyUniversity Hospital of Wales	United Kingdom
Riccardo Saccardi	Azienda Ospedaliera Universitaria CareggiCell Therapy and Transfusion Medicine Unit	Italy
Franca Fagioli	Onco-Ematologia PediatricaCentro Trapianti Cellule Staminali	Italy
Simona Sica	Universita Cattolica S. CuoreIstituto di Ematologia	Italy
Hildegard Greinix	LKH - University Hospital GrazLKH - University Hospital Graz	Austria
José Luis López Lorenzo	Fundación Jiménez DíazHematología	Spain
José Mª Moraleda	Hospital Universitario Virgen de la ArrixacaCtra. Madrid - Cartagena	Spain
Corrado Tarella	European Institute of OncologyInstitute of Haematology	Italy
Wu Ka Lung	ZNALange Beeldekensstraat 267	Belgium
Stefania Bramanti	Istituto Clinico HumanitasTransplantation Unit	Italy
Juan Pio Torres Carrete	Complejo Hospitalario de A CoruñaHematologia (Planta 11ª)	Spain
Ali Bazarbachi	Department of Internal MedicineAmerican University of Beirut Medical Center	Lebanon
Joaquin Martínez López	Hospital Univ. 12 de OctubreServicio de Hematología	Spain
Rachel Protheroe	Bristol Royal Hospital for ChildrenDept. of Paediatric Oncology/BMT	United Kingdom
Charles Craddock	University Hospital Birmingham NHSTrustQueen Elizabeth Medical Centre, Edgbaston	United Kingdom
Luca Castagna	U.O.D Trapianti di midollo osseoA.O.R Villa Sofia-Cervello	Italy
Mahmoud Aljurf	King Faisal Specialist Hospital & Research CentreOncology (Section of Adult Haematolgy/BMT)	Saudi Arabia
Moshe Yeshurun	Beilinson HospitalHematology and BMT Department	Israel
Carmen Albo López	Hospital Álvaro Cunqueiro - Complejo Hospitalario Universitario de VigoServicio de Hematología	Spain
Sebastian Giebel	Department of Bone Marrow Transplantation and OncohematologyMaria Sklodowska-Curie National Research Institute of Oncology	Poland
Aloysius Ho	Singapore General Hospital20 College Road	Singapore
Andrew McDonald	ALBERTS CELLULAR THERAPYNetcare Pretoria East Hospital	South Africa
D. Selleslag	A.Z. Sint-JanDept. of Hematology	Belgium
Estelle Verburgh	University of Cape Town Faculty of Health Sciences, Division of Clinical Haematology	South Africa
Johanna Tischer	Klinikum Grosshadern, Medizinische Klinik III	Germany
Urpu Salmenniemi	HUCH Comprehensive Cancer Center, Stem Cell Transplantation Unit	Finland
Peter Dreger	University of Heidelberg, Medizinische Klinik u. Poliklinik V	Germany
Angelo Michele Carella	IRCCS, Casa Sollievo della Sofferenza, Department of Hemato-Oncology	Italy
Guiseppe Visani	AORMN Hospita, lHematology & Transplant Centre	Italy
Christof Scheid	University of Cologne I, Department of Medicine	Germany
Maria del Mar Perera Alvarez	Hospital de Gran Canaria, Dr Negrin`Servicio de Hematología y Hemoterapia	Spain
Péter Reményi	Dél-pesti Centrumkórház–Országos Hematológiai és Infektológiai Intézet	Hungary
Mareike Verbeek	Klinikum Rechts der Isar III, Medizinische Klinik der TU	Germany
Gwendolyn Van Gorkom	University Hospital Maastricht, Department of Internal Medicne, Hematology /Oncology	The Netherlands
Charles Crawley	Addenbrookes Hospital, Department of Haematology	United Kingdom
Sonia Gonzalez Pérez	Hospital Clinico Universitario, Servicio de Hematología	Spain
Edgar Faber	Nadace Haimom University Hospital	Czech Republic
Maite Zudaire	Unidad de Ensayos Clínicos de Hematología Pabellón A, bajo, Complejo Hospitalario de Navarra	Spain
Abdelghani Tbakhi	King Hussein Cancer Centre, Aljubiha	Jordan
David Valcárcel	Hospital Vall d`Hebron, Unidad de Adultos	Spain
Massimo Martino	Grande Ospedale Metropolitano Bianchi Melacrino Morelli, Centro Unico	Italy
Ellen Meijer	VU University Medical Center, Department of Hematology	The Netherlands
Hakan Ozdogu	Baskent University Hospital, Haematology Division, BMT Unit	Turkey
Johannes Clausen	Elisabethinen-Hospital I, Internal Medicine Department	Austria
Carlos Vallejo Llamas	Hospital Universitario Donostia Beguiristain	Spain
Eleni Tholouli	Manchester Royal Infirmary, Clinical Haematology Department	United Kingdom
Nicola Mordini	Az. Ospedaliera S. Croce e Carle, Division of Hematology	Italy
Josep Maria Ribera Santasusana	ICO-Hospital Universitari Germans Trias i Pujol, Cattedra e Servizio di Ematologia	Spain
Nicolaus Kröger	University Hospital Eppendorf, Bone Marrow Transplantation Centre	Germany
Javier López-Jiménez	Hospital Ramón y Cajal, Servicio de Hematología	Spain
Dimitrios Karakasis	Evangelismos Hospital, Division of Hematology, BMT Unit	Greece
Fabio Benedetti	Policlinico G.B. Rossi, Divisione di Ematologia, Unità di TMO	Italy
Anne Huynh	CHU-Institut Universitaire du Cancer Toulouse, Oncopole	France
Kerstin Schäfer-Eckart	Klinikum Nuernberg 5, Medizinische Klinik, BMT Unit	Germany
Filiz Vural	Ege University Medical School, Department of Hematology	Turkey
Rik Schots	Universitair Ziekenhuis Brussel, Division of Clinical Hematology	Belgium
Ashrafsadat Mousavi	Shariati Hospital, Hematology-Oncology and BMT Research	Iran
Dries Deeren	AZ Delta, Hematology Department	Belgium
Paola Carluccio	U.O. Ematologia con Trapianto, Azienda Ospedaliero Universitaria Policlinico Bari	Italy
Mathilde Hunault-Berger	CHRU, Service des Maladies du Sang	France
Alessandro Rambaldi	Asst Papa Giovanni XXIII, Hematology and Bone Marrow Transplant Unit	Italy
Gaelle Guillerm	CHRU de Brest 2	France
Francesco Merli	Arcispedale S. Maria Nuova, Unita Operativa Ematologia	Italy
Jaime Sanz	University Hospital La Fe, Hematology Departmenta 7	Spain
Jean-Valère Malfuson	Hôpital Percy, Hematology Department	France
Jean Henri Bourhis	Gustave Roussy Cancer Campus, BMT Service, Department of Hematology	France
Hélène Labussière-Wallet	Centre Hospitalier Lyon Sud, Pavillon Marcel Bérard -Bat 1G	France
Bruno Lioure	Techniciens d`Etude Clinique suivi de patients greffes, Nouvel Hopital Civil	France
Maurizio Musso	Ospedale La Maddalena, Department Oncologico, Unità Operativa di Oncoematologia	Italy

(*continued*)

Kazimierz Halaburda	Institute of Hematology and Transfusion Medicine I	Poland
Rose-Marie Hamladji	Centre Pierre et Marie Curie, Service Hématologie Greffe de Moëlle	Algeria
Renato Fanin	Azienda Ospedaliero Universitaria di Udine, Division of Hematology	Italy
Murray Martin	Leicester Royal Infirmary, Department of Haematology	United Kingdom
Pavel Jindra	Charles University Hospital, Department of Hematology/Oncology	Czech Republic
Antonia Sampol Mayol	Fundació Institut d`Investigació Sanitària Illes Balears – IdISBa Hospital Universitari Son Espases	Spain
Aleksandr Kulagin	First State Pavlov Medical University of St. Petersburg, Raisa Gorbacheva Memorial Research Institute for Paediatric Oncology, Hematology, and Transplantation	Russia
Yves Beguin	University of Liege, Department of Hematology	Belgium
Rafael Duarte	Clinica Puerta de Hierro, Servicio de Hematologia y Hemoterapia	Spain
Antonio Perez Martinez	Hospital Universitario La Paz, Hematologia-Oncologia	Spain
Inmaculada Heras	Hospital Morales Meseguer	Spain
Jose Rifón	Clínica Universitaria de Navarra, Area de Terápia Celular	Spain
Jörg Cammenga	University Hospital, Department of Hematology	Sweden
Alberto Mussetti	ICO–Hospital Duran i Reynals	Spain
Victoria Potter	Kings College Hospital, Department of Hematological Medicine	United Kingdom
Fabrizio Pane	University of Napoli`Federico II Medical School	Italy
John Gribben	St. Bartholomew`s and The Royal London NHS Trust45 Little Britain	United Kingdom
Jose Antonio Pérez-Simón	Hospital Universitario Virgen del RocíoServicio de Hematologia y Hemoterapia	Spain
Mohamad Mohty	Hopital Saint AntoineDepartment of Hematology	France
Mohamad Mohty	Hopital Saint AntoineDepartment of Hematology	France
John Snowden	Sheffield Teaching Hospitals NHS TrustSouth Yorkshire Region (Adult) BMT Programme	United Kingdom
Adrian Bloor	Christie NHS Trust HospitalAdult Leukaemia and Bone Marrow Transplant Unit	United Kingdom
Marieke Dürholt	Evangelisches Krankenhaus Essen-Werden gGmbH, Haematologie/Onkologie/ Stammzelltransplantation	Germany
Eva Maria Wagner-Drouet	University Medical Center Mainz	Germany
Attilio Olivieri	Azienda Ospedali Riuniti di Ancona, Department of Hematology	Italy
Giuseppe Milone	Ospedale Policlinico, Programma di Trapianto Emopoietico Misto e Metropolitano Di Catania	Italy
Mario Petrini	Azienda Ospedaliero Universitaria Pisana, Unità Operativa Ematologia	Italy
Marco Ruggeri	S. Bortolo Hospital, Department of Hematology	Italy
Jan Zaucha	Medical University of Gdansk, University Hospital	Poland
M. Bornhäuser	Universitaetsklinikum Dresden, Medizinische Klinik und Poliklinik I	Germany
Wolf Rösler	University Hospital Erlangen, Department of Internal Medicine 5	Germany
Jürgen Finke	University of Freiburg, Department of Medicine, Hematology, Oncology	Germany
Giorgio La Nasa	Centro Trapianti Unico Di CSE Adulti e Pediatrico	Italy
Marco Ladetto	Azienda Ospedaliera Nazionale SS Antonio e Biagio, Haematology Department	Italy
Michele Cimminiello	Ospedale San Carlo, Department of Hematology	Italy
Nathalie Fegueux	CHU Lapeyronie, Département d`Hématologie Clinique	France
Herve Tilly	Centre Henri Becquerel, Hematology	France
Amandine Charbonnier	University of Amiens, CHU Amiens, Service d`Hematologie	France
Pascal Turlure	CHRU Limoges, Service d`Hématologie Clinique	France
Nabil Yafour	University Hospital of Oran, Department of Haematology and Cell Therapy	Algeria
Mutlu Arat	Demiroglu Bilim University Istanbul, Florence Nightingale Hospital, Hematopoietic SCT Unit	Turkey

Authorship statement: A.R., E.G., A.N., M.M. designed the study; D.B., F.C., J.D.M., J.J.C., P.C., F.S.G., E.N., L.C., E.F., J.K., M.R., Y.K., J.P., Z.G., J.V., F.B., J.S., A.S., and B.P. provided cases for the study; J.E.G. and M.L. analyzed data and performed the statistical analysis; A.R. and H.R. wrote the manuscript; and all authors edited and approved the final manuscript for publication.

SUPPLEMENTARY MATERIALS

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