ARTICLE

Post-transplant cyclophosphamide *versus* anti-thymocyte globulin as graft- *versus*-host disease prophylaxis in haploidentical transplant

Annalisa Ruggeri,[1] Yuqian Sun,[2] Myriam Labopin,[1,3] Andrea Bacigalupo,[4] Francesca Lorentino,[5] William Arcese,[6] Stella Santarone,[7] Zafer Gülbas,[8] Didier Blaise,[9] Giuseppe Messina,[10] Ardeshi Ghavamzadeh,[11] Florent Malard,[1] Benedetto Bruno,[12] Jose Luis Diez-Martin,[13] Yener Koc,[14] Fabio Ciceri,[5] Mohamad Mohty*[1,3,15] and Arnon Nagler*[15,16,17]

[1]Service d'Hématologie et Thérapie Cellulaire, Hôpital Saint Antoine, AP-HP, Paris, France; [2]Peking University People's Hospital, Peking University Institute of Hematology, Beijing, China; [3]INSERM, UMRs 938, Paris, France; [4]Ospedale San Martino, Department of Haematology II, Genova, Italy; [5]Ospedale San Raffaele, Haematology and BMT, Milano, Italy; [6]Tor Vergata University, Stem Cell Transplant Unit, Policlinico Universitario Tor Vergata, Rome, Italy; [7]Ospedale Civile Dipartimento di Ematologia, Medicina Trasfusionale e Biotecnologie, Pescara, Italy; [8]Anadolu Medical Center Hospital, Bone Marrow Transplantation Department, Kocaeli, Turkey; [9]Programme de Transplantation & Therapie Cellulaire, Institut Paoli Calmettes, Marseille, France; [10]Centro Unico Regionale Trapianti, Alberto Neri, Bianchi-Melacrino-Morelli, Reggio Calabria, Italy; [11]Shariati Hospital, Hematology-Oncology and BMT Research, Teheran, Iran; [12]A.O.U Citta della Salute e della Scienza di Torino, Presidio Molinette, Torino, Italy; [13]Instituto de Investigacion Sanitaria Gregorio Marañon, Division of Hematology, Hospital Gregorio Marañon, Madrid, Spain; [14]Medical Park Hospitals, Stem Cell Transplant Unit, Antalya, Turkey; [15]Université Pierre et Marie Curie, Paris, France; [16]Division of Hematology and Bone Marrow Transplantation, The Chaim Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel; Tel Aviv University (TAU), Israel and [17]EBMT Paris Office, Hospital Saint Antoine, Paris, France

**MM and AN contributed equally to this work.*

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ABSTRACT

Severe graft-*versus*-host disease is a major barrier for non-T-cell-depleted haploidentical stem cell transplantation. There is no consensus on the optimal graft-*versus*-host disease prophylaxis. This study compared the two most commonly used graft-*versus*-host disease prophylaxis regimens (post-transplant cyclophosphamide-based *vs.* the anti-thymocyte globulin-based) in adults with acute myeloid leukemia reported to the European Society for Blood and Bone Marrow Transplantation. A total of 308 patients were analyzed; 193 received post-transplant cyclophosphamide-based regimen and 115 anti-thymocyte globulin-based regimen as anti-graft-*versus*-host disease prophylaxis. The post-transplant cyclophosphamide-based regimen was more likely to be associated to bone marrow as graft source (60% *vs.* 40%; *P*=0.01). Patients in the post-transplant cyclophosphamide-based regimen group had significantly less grade 3-4 acute graft-*versus*-host disease than those in the anti-thymocyte globulin-based group (5% *vs.* 12%, respectively; *P*=0.01), comparable to chronic graft-*versus*-host disease. Multivariate analysis showed that non-relapse mortality was lower in the post-transplant cyclophosphamide-based regimen group [22% *vs.* 30%, Hazard ratio (HR) 1.77(95%CI: 1.09-2.86); *P*=0.02] with no difference in relapse incidence. Patients receiving post-transplant cyclophosphamide-based regimen had better graft-*versus*-host disease-free, relapse-free survival [HR 1.45 (95%CI: 1.04-2.02); *P*=0.03] and leukemia-free survival [HR 1.48 (95%CI: 1.03-2.12); *P*=0.03] than those in the anti-thymocyte globulin-based group. In the multivariate analysis, there was also a trend for a higher overall survival [HR 1.43 (95%CI: 0.98-2.09); *P*=0.06] for post-trans-

Correspondence:
annalisa.ruggeri@aphp.fr

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plant cyclophosphamide-based regimen *versus* the anti-thymocyte globulin-based group. Notably, center experience was also associated with non-relapse mortality and graft-*versus*-host disease-free, relapse-free survival. Haplo-SCT using a post-transplant cyclophosphamide-based regimen can achieve better leukemia-free survival and graft-*versus*-host disease-free, relapse-free survival, lower incidence of graft-*versus*-host disease and non-relapse mortality as compared to anti-thymocyte globulin-based graft-*versus*-host disease prophylaxis in patients with acute myeloid leukemia.

Introduction

Allogeneic hematopoietic stem cell transplantation using a related haploidentical donor is an alternative option for patients lacking a fully matched sibling or a well matched unrelated donor.[1] However, due to the number of HLA mismatches, severe graft-*versus*-host disease (GvHD) is a major barrier for successful haploidentical stem cell transplantation (Haplo-SCT). T-cell depletion (TCD) has historically been successfully used to prevent severe lethal GvHD, but is limited by graft failure, delayed immune reconstitution, severe infections, and high incidence of relapse.[2,3] Other approaches, such as administration of additional post-transplant cell-therapies or optimization of the conditioning regimens helped to partially overcome these pitfalls, but were often associated with increased costs and with very experienced centers.[4,5] In recent years, unmanipulated haploidentical transplant with no *ex vivo* T-cell depletion emerged as a viable option and has been performed with increasing frequency and success.[6-12] Among the several methods for GvHD prevention, anti-thymocyte globulin (ATG) or post-transplant high-dose cyclophosphamide (PTCY) are the most effective prophylaxis strategies.[13] ATG includes a set of polyclonal antibodies directed against a wide range of immune cell epitopes that have been previously demonstrated to reduce GvHD incidence after allogeneic transplantation from both related and unrelated donors.[14-16] ATG allows extensive *in vivo* T-cell depletion and induces tolerance with expansion of regulatory T cells.[17]

More recently, high-dose PTCY (50 mg/kg days +3 and +4) has been introduced as an effective GvHD prophylaxis by Luznik *et al.*,[9] based on the rationale that cyclophosphamide is non-toxic to hematopoietic stem cells and can selectively deplete the alloreactive T cells.[18] Both approaches have resulted in very low incidence of GvHD post Haplo-SCT, despite the broad HLA disparities. Most publications are mostly from single center studies on various, usually heterogenous, hematologic diseases.[6,8,9,19] However, there is no consensus on the GvHD prophylaxis regimen in the setting of non-T-cell depleted Haplo-SCT using bone marrow (BM) or peripheral blood stem cells (PBSC). The current study aimed to compare these two approaches for GvHD prophylaxis in patients with acute myeloid leukemia (AML) in complete remission (CR) reported to the European Group for Blood and Marrow Transplantation (EBMT) registry.

Table 1. Details of graft-*versus*-host disease prophylaxis.

GvHD prevention	PTCY group	ATG group
PTCY	21	0
PTCY+CSA+MMF	119	0
PTCY+TACRO+MMF	53	0
CSA+MTX	0	23
CSA+MMF	0	8
CSA+MMF+MTX	0	8
CSA+MMF+MTX+BASI	0	40
TACRO+MMF	0	5
SIRO+MMF	0	31
Total	193	115

GvHD: graft-*versus*-host disease; PTCY: post-transplant cyclophosphamide; ATG: antithymocyte globulin; CSA: cyclosporine; MMF: mycophenolate mofetil; TACRO: tacrolimus; MTX: methotrexate; BASI: basiliximab; SIRO: sirolimus.

Methods

Study design

We analyzed all adults (age >18 years) with AML in first or second CR (CR1 or CR2) at transplant, reported to the "Promise" database, who underwent a Haplo-SCT as first allogeneic SCT between January 2007 and July 2014. Haplo was defined as recipient-donor number of HLA mismatches over 2. For GvHD prophylaxis, patients received PTCY- or ATG-based treatment. For the purpose of comparison, the PTCY group consisted of PTCY alone or PTCY plus other agents (Table 1). Similarly, the ATG group included patients who received ATG with or without other drugs (Table 1). Patients who were simultaneously treated with PTCY and ATG were excluded (n=13). A total of 308 patients were reported from 78 transplant centers, including 193 patients in the PTCY and 115 in the ATG group. Eight centers contributed 10 or more patients. All patients or legal guardians provided informed consent for Haplo-SCT according to the Declaration of Helsinki. The Review Board of the Acute Leukemia Working Group of the EBMT approved this study.

Definitions and statistical analysis

The primary end point was leukemia-free survival (LFS). Secondary end points were acute GvHD (aGvHD) and chronic GvHD (cGvHD), relapse incidence (RI), non-relapse mortality (NRM), GvHD-free, relapse-free survival (GRFS)[20,21] and overall survival (OS). Refined GRFS was defined as survival without the following events: grade 3-4 acute GvHD, severe cGvHD, disease relapse, or death from any cause after Haplo-SCT. LFS was calculated until the date of first relapse, death from any cause or the last follow up for patients alive in CR. Relapse was defined as disease recurrence and appearance of blasts in the peripheral blood or BM (>5%) after CR. NRM was defined as death from any cause other than relapse. Acute GvHD was graded according to the modified Seattle Glucksberg criteria[23] and cGvHD according to the revised

Table 2. Characteristics of patients and donors.

Variables		PTCY group (n=193)	ATG group (n=115)	*P*
Follow up (months)	Median (range)	18 (2-61)	36 (3-84)	<0.001
Patient age (years)	Median (range)	49 (18.18-74.93)	46 (18.2-70.59)	0.383
Donor age (years)	Median (range)	34.5(13.08-72.14)	34.05(14.11-70.77)	0.799
Female donor to male patient	Yes	48 (24.87%)	38 (33.33%)	0.110
Secondary AML	Yes	32 (16.58%)	19 (16.52%)	0.989
Cytogenetics status at Tx	Good	14 (7.25%)	10 (8.7%)	0.665
	Intermediate	56 (29.02%)	41 (35.65%)	
	Poor	12 (6.22%)	7 (6.09%)	
	NA/failed	79 (40.93%)	38 (33.04%)	
	Secondary AML	32 (16.58%)	19 (16.52%)	
Disease status at Tx	CR1	118 (61.14%)	73 (63.48%)	0.716
	CR2	75 (38.86%)	42 (36.52%)	
Karnofsky at Tx	≥80%	170 (95.51%)	107 (98.17%)	0.327
Stem cell source	BM	116 (60.1%)	53 (46.09%)	0.016
	PB	77 (39.9%)	62 (53.91%)	
Conditioning	MAC	110 (56.99%)	62 (53.91%)	0.598
	TBF	50	33	
	RIC	83 (43.01%)	53 (46.09%)	
	TBF	18	12	
	Treo+Flu	1	15	
	Cy+Flu+TBI	19	16	
	Cy TBI	34	0	
CMV D/R	neg to neg	18 (9.68%)	9 (8.04%)	0.908
	pos to neg	10 (5.38%)	5 (4.46%)	
	neg to pos	34 (18.28%)	19 (16.96%)	
	pos to pos	124 (66.67%)	79 (70.54%)	

PTCY: post-transplant cyclophosphamide; ATG: antithymocyte globulin; AML: acute myeloid leukemia; Tx: transplant; NA, not available; CR1: first complete remission; CR2: second complete remission; BM: bone marrow; PB: peripheral blood; MAC: myeloablative conditioning; TBF: thiotepa+busulfan+fludarabine; RIC: reduced intensity conditioning; Treo: treosulfan; Cy: cyclophosphamide; Flu: fludarabine; TBI: total body irradiation; CMV: cytomegalovirus; neg: negative; pos: positive; D: donor; R: recipient.

Seattle criteria.[24] The risk stratification of AML at diagnosis was established according to the National Comprehensive Cancer Network guideline (v.1.2015).

Myeloablative conditioning regimen (MAC) was defined as a regimen containing either total body irradiation (TBI) with a dose greater than 6 Gray, a total dose of oral busulfan (Bu) greater than 8 mg/kg, or a total dose of intravenous Bu greater than 6.4 mg/kg or melphalan at doses of 140 mg/m^2 or more. In addition, regimens containing two alkylating agents were considered as MAC. All other regimens were defined as reduced intensity conditioning (RIC). Patients received rabbit ATG (FreseniusTM) (75%) or thymoglobulin (25%).

The median dose of ATG was 20 mg/Kg [interquartile range (IQR) 20-30 mg/Kg] for FreseniusTM and 10 mg/Kg (IQR: 10-10) for thymoglobulin.

GRFS, LFS and OS were estimated by the Kaplan-Meier method. Cumulative incidence (CI) functions were used to estimate aGvHD, cGvHD, RI and NRM. Competing risks were death for RI, relapse for NRM, relapse or death for aGvHD and cGvHD. Univariate analyses were carried out using the log-rank test for GRFS, OS and LFS, and Gray's test for CI.

For univariate analysis, comparisons were made by using χ^2 tests for categorical and Mann-Whitney tests for continuous variables. Multivariate analyses were performed using the Cox proportional hazard model. Type of GvHD prophylaxis, disease status, age at transplant, type of AML, graft source, conditioning and center experience were included in the final model. The significance level was fixed at 0.05, and *P* values were two-sided. Statistical analyses were performed with the SPSS 19 (SPSS Inc./IBM, Armonk, NY, USA) and R 3.0.1 (R Development Core Team, Vienna, Austria) software packages.

Results

Patients' and transplant characteristics

Patients' and transplant characteristics are summarized in Table 2. One hundred and ninety-three patients received PTCY- and 115 ATG-based GvHD prophylaxis. The median age at Haplo-SCT was 49 and 45 years for the PTCY and ATG groups, respectively (*P*=0.38). Of the 308 patients, 61% in the PTCY and 63% in the ATG group were transplanted in CR1 (*P*=0.71). There was no difference in the conditioning regimen; this was MAC in more than 50% of cases in both groups (*P*=0.59). Patients receiving PTCY were more likely to receive BM as the graft source (60.1% *vs.* 39.9%; *P*=0.01), and had shorter follow up (18 *vs.* 36 months; *P*<0.001) (Table 2).

In the PTCY group, the most common combination (61.7%) was PTCY plus cyclosporine A (CSA) and mycophenolate mofetil (MMF), whereas it was PTCY plus tacrolimus and MMF in 27.5% of the patients. In the ATG group, the GvHD prophylaxis varied from a combination of 3-5 drugs; the most common (34.8%) regimen was a 5-drug combination of ATG with CSA and MMF, methotrexate (MTX) and basiliximab (Table 1).

Table 3. Univariate analysis for 2-year outcomes.

2-year outcome	RI % [95% CI]	NRM % [95% CI]	LFS % [95% CI]	OS % [95% CI]	aGvHD gr III-IV % [95% CI]	cGvHD % [95% CI]	ext. cGvHD% [95% CI]	GRFS % [95% CI]
PTCY	21.6% [15.6-28.3]	22.4% [16.3-29]	56% [48.2-63.8]	58% [49.9-66.1]	4.7% [2.3-8.4]	33.7% [26.4-41.1]	8.6% [4.9-13.6]	50.9% [43.2-58.7]
ATG	22.3% [14.7-30.9]	30.5% [23.7-37.5]	47.2% [37.5-56.9]	54.2% [44.4-63.9]	12.5% [7.1-19.3]	28.3% [19.8-37.3]	12.6% [7-19.9]	38.9% [29.3-48.5]
P	0.97	0.19	0.26	0.37	0.01	0.33	0.26	0.07
age<50	22.8% [16.1-30.1]	25.2% [18.5-32.5]	52% [43.6-60.4]	58.3% [49.9-66.8]	8.7% [5-13.7]	36.7% [28.7-44.6]	12.4% [7.5-18.7]	42.3% [33.8-50.8]
Age>50	22% [14.9-30]	25.6% [18.8-32.9]	52.4% [43.4-61.5]	55% [45.9-64.1]	6.5% [3.2-11.4]	26% [18.5-34.1]	7.7% [3.9-13.1]	49.9% [41.1-58.8]
P	0.80	0.95	0.93	0.61	0.42	0.10	0.40	0.39
M	21.9% [15.3-29.2]	26.6% [19.8-33.9]	51.5% [43.1-59.9]	57.1% [48.8-65.4]	6% [3.1-10.4]	34.8% [27.2-42.6]	9% [5-14.5]	46% [37.6-54.3]
PB	22.9% [15.8-30.9]	24% [17.4-31.2]	53.1% [44-62.1]	56.1% [46.7-65.4]	9.6% [5.4-15.3]	27.8% [19.8-36.3]	12% [6.7-18.8]	45.6% [36.5-54.7]
P	0.50	0.90	0.62	0.48	0.21	0.14	0.52	0.38
CR1	21.2% [15.2-27.9]	24.2% [18-30.9]	54.6% [46.8-62.4]	59.5% [51.8-67.3]	6.4% [3.5-10.5]	33.3% [26.2-40.6]	11.2% [6.9-16.8]	47.2% [39.3-55.1]
CR2	24.5% [16.2-33.8]	27.7% [21.2-34.5]	47.8% [37.6-58]	51.7% [41.3-62]	9.7% [5.1-16.1]	29.3% [20.4-38.8]	8.4% [4.1-14.7]	43.5% [33.5-53.4]
P	0.69	0.46	0.83	0.52	0.29	0.69	0.86	0.85
Female to male	23.4% [14.7-33.2]	25.3% [19.4-31.5]	51.4% [40.1-62.6]	53.6% [42-65.3]	7.2% [2.9-14.1]	32.9% [22.8-43.3]	12.9% [6.5-21.6]	44.6% [33.4-55.7]
Other	22.1% [16.2-28.7]	24.9% [19.1-31.2]	52.9% [45.5-60.3]	58.5% [51.3-65.8]	7.8% [4.7-11.9]	31.6% [24.8-38.6]	9.1% [5.5-13.9]	46.8% [39.3-54.2]
P	0.83	0.83	0.87	0.83	0.84	0.84	0.31	0.89
Patient CMV neg	24.5% [10.1-42.3]	25.2% [12.8-39.6]	50.3% [32.1-68.5]	60.2% [43-77.3]	5% [0.9-15]	32.8% [16.8-49.9]	5.5% [1-16.5]	50.7% [32.5-68.9]
Patient CMV pos	22.4% [17.1-28.1]	24.7% [12.5-39.1]	52.9% [46.3-59.5]	56.8% [50.1-63.5]	8.3% [5.3-12.1]	30.4% [24.4-36.5]	10.2% [6.6-14.7]	45.8% [39.2-52.4]
P	0.57	0.80	0.80	0.63	0.46	0.92	0.35	0.26
Donor CMV neg	32.3% [21-44.1]	19.9% [11.6-29.8]	47.8% [35.4-60.2]	52.7% [40.5-65]	6.4% [2.4-13.4]	34.3% [22.7-46.3]	9.8% [4.2-18.1]	43.7% [31.5-55.8]
Donor CMV pos	19.2% [13.8-25.3]	27.1% [17.6-37.6]	53.6% [46.4-60.9]	58.3% [51.1-65.6]	8.4% [5.1-12.6]	29.9% [23.5-36.4]	9.5% [5.8-14.2]	46.8% [39.5-54.1]
P	0.03	0.29	0.41	0.58	0.59	0.80	0.99	0.47
Good	9.5% [1.5-26.9]	12.7% [2-33.7]	77.8% [60.4-95.1]	81.1% [63.9-98.2]	0 –	43.1% [22-62.7]	14.3% [3.2-33.1]	63.3% [42.6-84]
Interm	30.8% [21-41.2]	29.6% [9.9-52.6]	39.6% [28.7-50.4]	47.1% [35.9-58.3]	9.5% [4.6-16.4]	24.1% [15.4-33.7]	8.3% [3.5-15.7]	36.9% [26.2-47.7]
Poor	24.7% [7.1-47.8]	23.5% [6.4-46.6]	51.8% [27.4-76.3]	55.9% [30.8-81.1]	10.5% [1.7-29]	38.4% [14.6-62.1]	11.8% [1.7-32.5]	46.1% [21.6-70.5]
NA/failed	17.1% [10.2-25.4]	27.8% [8.8-50.9]	55.1% [45-65.3]	57.5% [47.4-67.6]	8.8% [4.5-15]	37.6% [27.8-47.3]	13.9% [7.7-21.8]	44.1% [33.8-54.5]
Sec. AML	22.4% [11.3-35.9]	18.6% [4.1-41.2]	58.9% [44.4-73.4]	62.4% [47.8-77]	4% [0.7-12.3]	26.5% [14.3-40.4]	4.3% [0.8-13.2]	57.9% [43.6-72.1]
P	0.25	0.45	0.10	0.28	0.41	0.14	0.50	0.2
De novo	22.4% [17-28.4]	26.9% [21.2-32.8]	50.7% [43.9-57.5]	55.4% [48.5-62.3]	8.4% [5.4-12.2]	32.9% [26.7-39.2]	11.5% [7.6-16.3]	43.2% [36.3-50]
Secondary	22.4% [11.3-35.9]	18.6% [13.8-24.1]	58.9% [44.4-73.4]	62.4% [47.8-77]	4% [0.7-12.3]	26.5% [14.3-40.4]	4.3% [0.8-13.2]	57.9% [43.6-72.1]
P	0.75	0.27	0.48	0.58	0.27	0.39	0.14	0.18
Nb haplo in Center<10	23.6% [16.5-31.4]	30.9% [23-39.1]	45.5% [36.5-54.5]	50.4% [41.5-59.3]	4.8% [2.1-9.2]	22.3% [15.1-30.3]	8.3% [4.1-14.2]	43% [34.1-51.9]
Nb haplo In center>10	20.9% [14.4-28.2]	20.7% [13.9-28.5]	58.4% [50.1-66.7]	59.6% [51.2-68.1]	10.2% [6.1-15.5]	40% [31.9-47.9]	12% [7.3-18.1]	48.5% [40-57]
P	0.39	0.06	0.02	0.12	0.08	0.0002	0.20	0.41

y: years; RI: relapse incidence; CI: confidence interval; NRM: non-relapse mortality; LFS: leukemia-free survival; OS: overall survival; aGvHD: acute graft-versus-host-disease; cGvHD: chronic graft-versus-host-disease; GRFS; GvHD-free, relapse-free survival; PTCY: post-transplant cyclophosphamide; ATG: anti-thymocyte globulin; BM: bone marrow; PB: peripheral blood; CR: complete remission; CMV: cytomegalovirus; interm: intermediate; NA: not available; sec.: secondary; AML: acute myeloid leukemia; nb: number; haplo: haplo-identical allogeneic stem cell transplantation; pos: positive; neg: negative; M: male.

Table 4. Multivariate analysis for outcomes.

		P	HR	CI lower	CI upper
LFS	ATG *vs.* PT-Cy	0.03	1.48	1.03	2.12
	CR2 *vs.* CR1	0.53	1.12	0.78	1.61
	Age at Tx (per 10 years)	0.20	1.09	0.95	1.25
	Secondary AML	0.25	0.74	0.44	1.25
	PB *vs.* BM	0.81	1.04	0.73	1.49
	RIC *vs.* MAC	0.81	0.96	0.66	1.39
	Nb haplo done in the center during the period study	<0.001	0.97	0.96	0.99
GRFS	ATG *vs.* PT-Cy	0.03	1.45	1.04	2.02
	CR2 *vs.* CR1	0.64	1.08	0.77	1.52
	Age at Tx (per 10 years)	0.58	1.04	0.91	1.17
	Secondary AML	0.14	0.69	0.41	1.14
	PB *vs.* BM	0.48	1.13	0.81	1.58
	RIC *vs.* MAC	0.86	0.97	0.68	1.38
	Nb haplo done in the center during the period study	0.04	0.99	0.97	1.00
OS	ATG *vs.* PT-Cy	0.06	1.43	0.98	2.09
	CR2 *vs.* CR1	0.20	1.27	0.88	1.85
	Age at Tx (per 10 years)	0.15	1.11	0.96	1.28
	Secondary AML	0.32	0.76	0.44	1.31
	PB *vs.* BM	0.71	1.07	0.74	1.56
	RIC *vs.* MAC	0.72	0.93	0.63	1.38
	Nb haplo done in the center during the period study	<0.001	0.97	0.95	0.98
RI	ATG *vs.* PT-Cy	0.58	1.17	0.67	2.02
	CR2 *vs.* CR1	0.59	1.16	0.67	1.98
	Age at Tx (per 10 years)	0.70	1.04	0.85	1.27
	Secondary AML	0.91	0.96	0.46	2.00
	PB *vs.* BM	0.66	1.13	0.66	1.92
	RIC *vs.* MAC	0.68	1.12	0.64	1.96
	Nb haplo done in the center during the period study	0.14	0.98	0.96	1.01
NRM	ATG *vs.* PT-Cy	0.02	1.77	1.09	2.86
	CR2 *vs.* CR1	0.73	1.09	0.67	1.76
	Age at Tx (per 10 years)	0.18	1.13	0.94	1.36
	Secondary AML	0.15	0.58	0.27	1.24
	PB *vs.* BM	0.90	0.97	0.60	1.57
	RIC *vs.* MAC	0.52	0.85	0.51	1.41
	Nb haplo done in the center during the period study	<0.001	0.96	0.94	0.98
aGVHD II-IV	ATG *vs.* PT-Cy	0.13	1.43	0.90	2.20
	CR2 *vs.* CR1	0.36	1.25	0.78	2.00
	Age at Tx (per 10 years)	0.77	1.00	0.98	1.02
	Secondary AML	0.51	1.25	0.65	2.38
	PB *vs.* BM	0.53	1.17	0.72	1.88
	RIC *vs.* MAC	0.98	0.99	0.60	1.65
	Nb haplo done in the center during the period study	0.94	1.00	0.98	1.02
aGVHD III-IV	ATG *vs.* PT-Cy	0.04	2.42	1.02	5.75
	CR2 *vs.* CR1	0.40	1.44	0.62	3.35
	Age at Tx (per 10 years)	0.22	0.82	0.59	1.13
	Secondary AML	0.57	0.64	0.14	3.02
	PB *vs.* BM	0.35	1.53	0.62	3.76
	RIC *vs.* MAC	0.97	1.02	0.39	2.67
	Nb haplo done in the center during the period study	0.49	1.01	0.98	1.05
cGVHD	ATG *vs.* PT-Cy	0.08	0.67	0.42	1.06
	CR2 *vs.* CR1	0.83	0.95	0.61	1.48
	Age at Tx (per 10 years)	0.40	0.93	0.79	1.10
	Secondary AML	0.70	0.88	0.44	1.72
	PB *vs.* BM	0.36	0.81	0.51	1.28
	RIC *vs.* MAC	0.51	0.85	0.52	1.38
	Nb haplo done in the center during the period study	<0.001	1.06	1.04	1.07
extensive GvHD	ATG *vs.* PT-Cy	0.37	1.43	0.65	3.11
	CR2 *vs.* CR1	0.81	0.91	0.41	2.02
	Age at Tx (per 10 years)	0.79	1.04	0.78	1.39
	Secondary AML	0.10	0.28	0.06	1.28
	PB *vs.* BM	0.31	1.52	0.68	3.39
	RIC *vs.* MAC	0.98	1.01	0.42	2.40
	Nb haplo done in the center during the period study	0.18	1.02	0.99	1.05

HR: hazard ratio; CI: confidence interval; LFS: leukemia-free survival; GRFS: GvHD-free, relapse-free survival; OS: overall survival; RI: relapse incidence; NRM: non-relapse mortality; aGVHD III-IV: grade III-IV acute graft-*versus*-host-disease; cGvHD: chronic graft-*versus*-host-disease; ATG: anti-thymocyte globulin; PT-CY: post-transplant cyclophosphamide; CR1: first complete remission; CR2: second complete remission; Tx: transplantation; AML: acute myeloid leukemia; PB: peripheral blood; BM: bone marrow; RIC: reduced intensity conditioning; MAC: myeloablative conditioning; haplo: hapo-identical stem cell transplantation; Nb: number.

GRFS, LFS and OS

The GRFS, LFS and OS at two years in the whole population were 45.7% (95%CI: 39.5%-51.9%), 52.9% (95%CI: 45.9%-58.3%) and 56.6% (95%CI: 50.46%-62.8%), respectively.

GRFS, LFS and OS were 50.9% (95%CI: 43.2%-58.7%) *versus* 38.9% (95%CI: 29.3%-48.5%) (P=0.07), 56% (95%CI: 48.2%-63.8%) *versus* 47.2% (95%CI: 37.5%-56.9%) (P=0.26) and 58% (95%CI: 49.9-66.1%) *versus* 54.2% (95%CI: 44.4%-63.9%) (P=0.37), for patients receiving PTCY *versus* ATG, respectively (Table 3 and Figure 1). According to disease status at Haplo-SCT, the 2-year LFS was 54.6% (95%CI: 46.8%-62.4%) for patients in CR1 and 47.8% (95%CI: 37.6%-58%) in CR2 (P=0.93). Detailed results of the univariate analysis are reported in Table 3.

Multivariate analysis (Table 4) showed a significantly lower LFS [HR 1.48; (95%CI: 1.03-2.12; P=0.034)], and GRFS [HR 1.45; (95%CI: 1.04-2.02; P=0.030)] for patients receiving ATG. In addition, another independent factor associated with outcomes was the increase in number of Haplo-SCT performed per year per transplant center (analyzed as a continuous variable) [LFS (HR 0.97; (95%CI: 0.96-0.99; P<0.001)], and GRFS [HR 0.99; (95%CI: 0.97-1.00; P<0.04)]. The center effect affected outcomes in both groups when analyzed separately (*data not shown*).

Graft-versus-host disease

The CI of grade 2-4 and grade 3-4 aGvHD at day 100 was 25% (95%CI: 20%-30%) and 7.6% (95%CI: 5%-11%), respectively. Grade 2-4 aGvHD was 21% for patients receiving ATG *versus* 31% for those with PT-Cy (P=0.07). Patients receiving PTCY as GvHD prophylaxis had significantly lower grade 3-4 aGvHD than those receiving ATG (4.7% *vs.* 12.5%; P=0.01) (Figure 2A). In the multivariate analysis (Table 4), the use of ATG was the only factor associated with occurrence of severe grade 3-4 aGvHD (HR 2.42; 95%CI: 1.20%-5.75%; P=0.04).

The CI of cGvHD and of extensive cGvHD at two years was 31.8% (95%CI: 26.2%-37.5%) and 10.2% (95%CI: 6.9%-14.4%), respectively. There was no difference in incidence of cGvHD (Figure 2B) between the two groups (95%CI: 33.7% *vs.* 28.3%; P=0.33), and for extensive cGvHD 8.6% *versus* 12.6% (P=0.26) for PTCY and ATG, respectively. In the multivariate analysis (Table 4), experience of the transplant center (increase in number of Haplo-SCT per year) was the only factor associated with total cGvHD (HR 1.06; 95%CI: 1.04-1.07; P<0.001).

Non-relapse mortality and relapse

The CI of 2-year NRM was 25.4% (95%CI: 20.4%-30.7%). In the multivariate analysis, the use of ATG as GvHD prophylaxis was an independent factor for higher NRM (HR 1.77; 95%CI: 1.09-2.86; P=0.02) (Figure 2C), as was also the center experience (HR 0.96; 95%CI: 0.94-0.98; P<0.001).

The CI of relapse at two years was 22.4% (95%CI: 17.4%-27.8%) in the whole population, and it was comparable between the two groups (21.6% *vs.* 22.3%; P=0.97) (Figure 2D). No factors were found to be associated with relapse in the multivariate analysis.

One hundred and twenty-two patients died, 62% of transplant-related causes and 38% due to disease recurrence. Infections and GvHD were the most common causes of NRM. There was no difference in causes of death between the two GvHD prophylaxis groups.

Discussion

The aim of our study was to compare the different GvHD prophylaxis in the non-TCD Haplo-SCT setting. In a homogenous population of AML in CR, we showed that the use of PTCY for GvHD prophylaxis was associated with better LFS and GRFS, similar relapse and cGvHD, less NRM and less severe aGvHD, than in the ATG group.

The incidence of grade 3-4 aGvHD in both groups is consistent with the previous reports in this setting. The largest study from Huang *et al*. reported a 10%-14% incidence of severe aGvHD in patients receiving ATG-based GvHD prophylaxis.[6,7] Other groups reported an incidence of grade 3-4 aGvHD ranging from 9±3% to 22±8% using the association of ATG with CSA, MTX plus MMF and

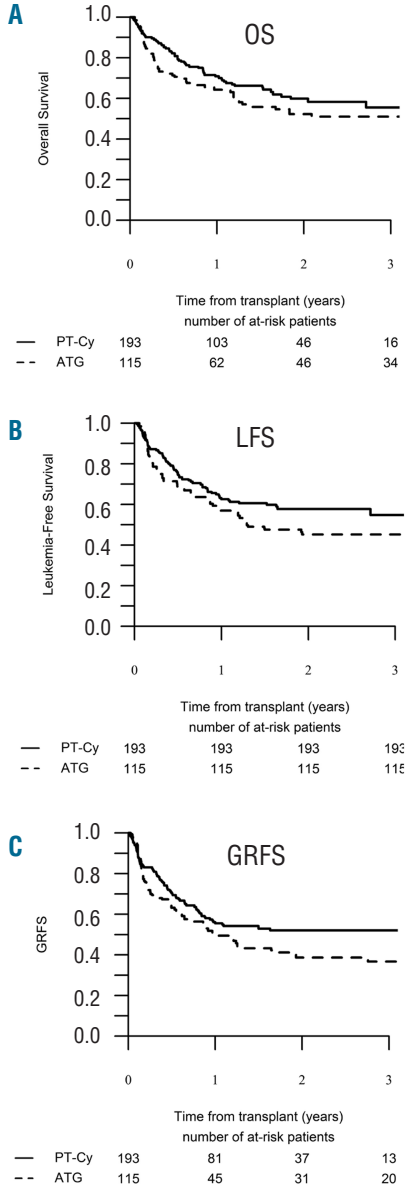

Figure 1. (A). Overall survival (OS), (B) leukemia-free survival (LFS), (C) graft-*versus*-host disease (GvHD)-free, relapse-free survival (GRFS) for post-transplant high-dose cyclophosphamide (PTCY)-based and anti-thymocyte globulin (ATG)-based GvHD prophylaxis.

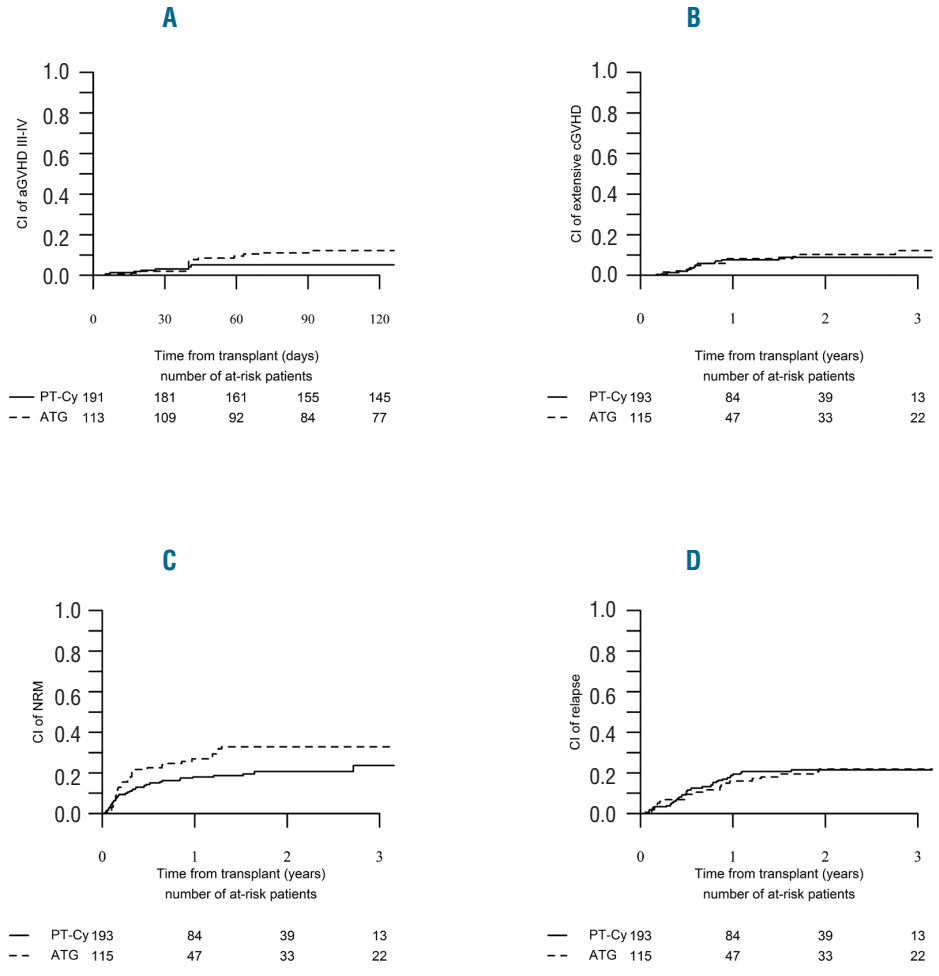

Figure 2. (A) Acute graft-*versus*-host disease (aGvHD) grade III-IV, (B) chronic graft-*versus*-host disease (cGvHD), (C) non-relapse mortality (NRM), and (D) relapse incidence (RI) for post-transplant high-dose cyclophosphamide (PTCY)-based and anti-thymocyte globulin (ATG)-based GvHD prophylaxis.

basiliximab[8,25] or sirolimus and MMF[26] as GvHD prophylaxis.

The PTCY regimen was first introduced by Luznik *et al.*[9,27] using PTCY with tacrolimus and MMF, BM graft and RIC conditioning, with a low 5% incidence of grade 3-4 aGvHD. This platform was rapidly adopted by other centers with similar results. Bacigalupo *et al.*[19] slightly modified the GvHD prophylaxis with PTCY (50 mg/kg days +3,+5) together with CSA and MMF, resulting in a 4% incidence of grade 3-4 aGvHD. The above historical data and the present retrospective study suggest that PTCY has a stronger effect in preventing severe GvHD. However, further prospective randomized studies are warranted to further confirm this conclusion. Despite the lower incidence in severe aGvHD in the PTCY group, we did not find an advantage in terms of cGvHD or extensive cGvHD. Notably, ATG has been recently shown to significantly reduce the incidence of cGvHD after allogeneic stem cell transplantation from related and unrelated donors.[15,28]

Importantly, in our series, there was no difference in the incidence of GvHD according to the source of stem cell. The use of BM or PBSC did not impact on the main outcomes both in the univariate and multivariate analysis.

The NRM in the PTCY group was lower than in ATG group. *In vivo* TCD is a known risk factor associated with high incidence of infection and NRM, as reported in adult patients with acute leukemia in the unrelated donor setting.[29] Moreover, a very favorable toxicity profile of PTCY Haplo-SCT has been observed, also in comparison with $CD34^+$ selected graft and ATG[30] and in the unmanipulated setting, in older patients.[31] Similarly, Kasamon *et al.* showed comparable NRM between younger patients and those over 70 years of age.[32]

A major concern related to the PTCY protocol is the high incidence of disease recurrence after transplantation. The reported RI after BM-RIC in patients with hematologic malignancies is up to 50%.[9] In our study, the relapse incidence in the PTCY group is lower than in previous reports. One possible explanation may be the fact that, in our study, patients were transplanted in CR1 or CR2 while in most previous reports, Haplo-SCT was mainly used as salvage treatment for advanced stage. Furthermore, we analyzed a homogenous series of patients with AML transplanted in CR, and including both RIC and MAC. In the latter setting, Bacigalupo *et al.*[19] reported 148 patients receiving PTCY Haplo-SCT, with an RI for patients in CR1 and CR2 of 11% and 26%, respectively.

Our study is the first to analyze the GRFS[22] in the setting

of Haplo-SCT. This end point has been already reported in the related and unrelated donor settings, and may reflect a better health status post transplantation and better quality of life. In our study, the different GvHD prophylaxis protocols had an impact on GRFS, with better results for the PTCY-based regimen, in the multivariate analysis. Longer Haplo-SCT follow up is needed to analyze the impact of this type of donor on long-term outcomes and complications.

Importantly, the center experience, in terms of number of Haplo-SCT performed per year, was another factor associated with NRM and GRFS. The center effect was also demonstrated by our group in the TCD setting both in children[33] and adults.[34] This effect may be due to the different management of post-transplant complications, life-threatening infections and relapse in each center. Until now, there has been no standard-of-care in the haploidentical setting, and the management of complications may vary significantly among different centers.

Our study has some limitations, being retrospective and encompassing a variety of conditioning regimens and GvHD prophylaxis; in addition, registry data on disease risk features are not complete.

One may argue for a potential period effect in transplant outcomes, with more Haplo-SCT using PT-CY being performed in more recent years. In our series, we reported patients transplanted between 2007 and 2014. Importantly, the major changes that lead to about 50% reduction in transplant-related mortality occurred before early 2000, as shown by Gooley *et al.*,[35] and there was no substantial change in transplant procedures and supportive care in this time period.

However, given the current unavailability of a prospective randomized trial, our registry-based survey allows consistent results in a large number of patients. In conclusion, for patients with AML in CR, non-TCD Haplo-SCT using PTCY with no ATG as GvHD prophylaxis allowed better LFS and GRFS, lower GvHD and lower NRM than ATG-based platforms, both using BM and PBSC and in the RIC and MAC setting. Further prospective randomized studies are warranted to support our conclusions.

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Participating center

Ospedale San Martino, Department of Haematology II, Genova, Italy; Ospedale San Raffaele s.r.l., Haematology and BMT, Milano, Italy; ¨Tor Vergata¨ University of Rome, Stem Cell Transplant Unit, Policlinico Universitario Tor Vergata, Rome, Italy; Ospedale Civile, Dipartimento di Ematologia, Medicina Trasfusionale e Biotecnologie, Pescara, Italy; Anadolu Medical Center Hospital, Bone Marrow Transplantation Department, Cumhuriyet Mah., Kocaeli, Turkey; Programme de Transplantation&Therapie Cellulaire, Centre de Recherche en Cancérologie de Marseille, Institut Paoli Calmettes, Marseille, France; Azienda Ospedaliera, Centro Unico Regionale Trapianti, Alberto Neri, Bianchi-Melacrino-Morelli, Reggio_Calabria, Italy; "Shariati Hospital; Hematology-Oncology and BMT Research", , Teheran, Iran; S.S.C.V.D Trapianto di Cellule Staminali, A.O.U Citta della Salute e della Scienza di Torino, Presidio Molinette, Torino, Italy; Hospital Gregorio Marañón, Sección de Trasplante de Medula Osea, Madrid, Spain; Medical Park Hospitals, Stem Cell Transplant Unit, Antalya, Turkey; Istituto Clinico Humanitas, Transplantation Unit, Department of Oncology and Haematology, Milano, Italy; Ospedale S. Camillo-Forlanini, Dept. of Hematology and BMT, Rome, Italy; Klinikum Grosshadern, Med. Klinik III, Munich, Germany; GKT School of Medicine, Dept. of Haematological Medicine, London, United Kingdom; Saint Petersburg State Medical Pavlov University, Ratsa Gorbacheva Memorial Children`s Institute, Hematology and Transplantology, St._Petersburg, Russia; Azienda Ospedali Riuniti di Ancona, Department of Hematology, Ancona University, Ancona, Italy; Ospedale A. Businco Cagliari, Haematology & Transplant Centre Wilma Deplano, Cagliari, Italy; University Hospital, Clinic of Hematology, Zürich, Switzerland; King Faisal Specialist Hospital & Research Centre, Oncology (Section of Adult Haematolgy/BMT), Riyadh, Saudi Arabia; AZ Delta, Hematology - Oncology Dept., Roeselare, Belgium; U.O. Ematologia con Trapianto, Azienda Ospedaliero Universitaria Policlinico Bari, Bari, Italy; Centre Pierre et Marie Curie, Service Hématologie Greffe de Moëlle, Alger, Algeria; Nottingham City Hospital, Hucknall Road, Nottingham, United Kingdom; University of Napoli, `Federico II` Medical School, Division of Hematology, Napoli, Italy; Unità Operativa Oncoematologia Pediatrica, Azienda Ospedaliera Universitaria Pisa, Pisa, Italy; Hospital Clinic, Institute of Hematology & Oncology, Dept. of Hematology, Barcelona, Spain; Hospital U. Marqués de Valdecilla, Servicio de Hematología-Hemoterapia, Santander, Spain; CHU Nantes, Dept. D`Hematologie, Nantes, France; Ospedale di Niguarda Ca` Granda, Hematology Department, Milano, Italy; U.O.S.A Centro Trapianti e Terapia Cellulare, Azienda Ospedaliera Universitaria Senese, Policlinico S.Maria alle Scotte, Siena, Italy; Ospedale Nord, Institute of Haematology, Taranto, Italy; Ospedale V. Cervello, Div. di Ematologia e Unità Trapianti, Palermo, Italy; University of Heidelberg, Medizinische Klinik u. Poliklinik V, Heidelberg, Germany; Ospedale San Gerardo, Clinica Ematologica dell`Universita Milano-Biocca, Monza, Italy; Dept. Haematology and Stem Cell Transplant, St. István and St. László Hospital, Semmelweis University St. Laszlo Campus, Budapest, Hungary; Az. Ospedaliera S. Croce e Carle, Division of Hematology, Cuneo, Italy; Azienda Ospedaliera Papa Giovanni XXIII, Hematology and Bone Marrow Transplant Unit, Bergamo, Italy; Universitaetsklinikum Dresden, Medizinische Klinik und Poliklinik I, Dresden, Germany; USD Trapianti di Midollo, Adulti, Pizzale Spedali Civili 1, Universita di Brescia, Brescia, Italy; Universitätsmedizin Mannheim, III. Medizinische Klinik, Einheit für Stammzelltransplantation, Mannheim, Germany; Klinik fuer Innere Medzin III, Universitätsklinikum Ulm, Ulm, Germany; Hospital Sirio-Libanes, Hematology Bone Marrow Transplant Unit,

Sao_Paulo, Brazil; Karolinska University Hospital, Dept. of Hematology, Stockholm, Sweden; Institut Jules Bordet, Experimental Hematology, Brussels, Belgium; Royal Free Hospital and School of Medicine, Department of Hematology, London, United Kingdom; Univ.`La Sapienza`, Dip. Biotecnologie Cellulari ed Ematologia, Rome, Italy; Bologna University, S.Orsola-Malpighi Hospital, Institute of Hematology & Medical, Oncology L & A Seràgnoli, Bologna, Italy; CHRU St. Etienne, Hopital Nord, Service d'Hematologie Clinique, Saint_Etienne, France; University Hospital, Dept. of Bone Marrow Transplantation, Essen, Germany; Hospital Santa Creu i Sant Pau, Hematology Department, Barcelona, Spain; Hôpitaux Universitaires de Genève, Département des Spécialités de Médecine, Service d'Hématologie, Geneva, Switzerland; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, IRCCS, Milano, Italy; University Hospital, Dept. of Medicine, Uppsala, Sweden; Hopital A. Michallon, Department of Hematology, Grenoble, France; Hospital Clínico Universitario, Servicio de Hematologia y Oncologia, Valencia, Spain; BMT unit, Clinica Ematologica, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; Hannover Medical School, Department of Haematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover, Germany; Hospital San Maurizio, Dept. of Hematology - BMT Unit, Bolzano, Italy; Universita Cattolica S. Cuore, Istituto di Ematologia, Ematologia, Rome, Italy; Deutsche Klinik für Diagnostik, KMT Zentrum, Wiesbaden, Germany; Ankara Bayindir Hospital, Haematology BMT, Ankara, Turkey; Pesaro Hospital, Hematology & Transplant Centre, Pesaro, Italy; Universitätsklinikum Göttingen, Abteilung Hämatologie und Onkologie, Gottingen, Germany; George Papanicolaou General Hospital, Haematology Department/BMT Unit, Thessaloniki, Greece; University of Milano, Istituto Nazionale dei Tumori, Hematology - Bone Marrow Transplantation Unit, Milano, Italy; Institut Universitaire du Cancer Toulouse, Oncopole, Toulouse, France; Ege University Medical School, Dept. of Hematology, Izmir, Turkey; Philipps Universitaet Marburg, University Hospital Giessen and Marburg, Marburg, Germany; Institute of Hematology and Blood Transfusion, Servicio de Hematología, Prague, Czech Republic; Azienda Ospedaliero Universitaria di Udine, Division of Hematology, Udine, Italy; Hospital Universitari Son Espases, Hematology Service, Palma_De_Mallorca, Spain; Umea University Hospital, Hematology, Umeå, Sweden; Chaim Sheba Medical Center, Chaim Sheba Medical Center, Dept. of Bone Marrow Transplantation, Tel-Hashomer, Israel; Hospital Universitario Virgen del Rocío, Servicio de Hematologia y Hemoterapia, Servicio Andaluz de Salud, Sevilla, Spain; "Ospedale Ferrarotto; Azienda Policlinico Vittorio Emanuele", Programma di Trapianto Emopoietico Misto e Metropolitano Di Catania, Ospedale Ferrarotto, Catania, Italy; Ospedale San Carlo, Dip. Ematologia, Potenza, Italy; Central Clinical Hospital, The Medical University of Warsaw, Department of Hematology & Oncol, Warsaw, Poland.

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