Allogeneic peripheral blood stem cell transplantation with anti-thymocyte globulin *versus* allogeneic bone marrow transplantation without anti-thymocyte globulin

Frédéric Baron,[1] Jacques-Emmanuel Galimard,[2-5] Myriam Labopin,[2-5] Ibrahim Yakoub-Agha,[6] Riitta Niittyvuopio,[7] Nicolaus Kröger,[8] Laimonas Griskevicius,[9] Depei Wu,[10] Edouard Forcade,[11] Carlos Richard,[12] Mahmoud Aljurf,[13] Grzegorz Helbig,[14] Hélène Labussière-Wallet,[15] Mohamad Mohty[2-5] and Arnon Nagler[2,16]

[1]Laboratory of Hematology, GIGA-I3, University of Liège and CHU of Liège, Liege, Belgium; [2]EBMT Paris study office/CEREST-TC, Paris, France; [3]Department of Haematology, Saint Antoine Hospital, Paris, France; [4]Sorbonne University, Centre De Recherche Saint Antoine, INSERM UMR938, Paris, France; [5]Sorbonne University, Paris, France; [6]University of Lille, INSERM, and CHU of Lille, INFINITE U1286, Lille, France; [7]HUCH Comprehensive Cancer Center, Stem Cell Transplantation Unit, Helsinki, Finland; [8]University Hospital Eppendorf, Bone Marrow Transplantation Center, Hamburg, Germany; [9]Institute of Clinical Medicine, Vilnius University and Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania; [10]First Affiliated Hospital of Soochow University, Department of Hematology, Suzhou, China; [11]CHU Bordeaux Hôpital Haut-Leveque, Pessac, France; [12]Hospital U. Marqués de Valdecilla, Servicio de Hematología-IDIVAL, Santander, Spain; [13]King Faisal Specialist Hospital & Research Centre Oncology, Riyadh, Saudi Arabia; [14]Silesian Medical Academy, University Department of Haematology and Bone Marrow Transplantation, Katowice, Poland; [15]Centre Hospitalier Lyon Sud, Service Hematologie, Lyon, France and [16]Division of Hematology and Bone Marrow Transplantation, The Chaim Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel

ABSTRACT

We compared severe graft-*versus*-host-disease (GvHD) free and relapse-free survival and other transplantation outcomes of acute myeloid leukemia (AML) patients given bone marrow (BM) without anti-thymocyte globulin (ATG) *versus* peripheral blood stem cells (PBSC) with ATG after myeloablative conditioning. In the cohort of patients receiving grafts from a human leukocyte antigen (HLA)-matched sibling donor, patients given PBSC with ATG (n=1,021) and those given BM without ATG (n=1,633) presented comparable severe GvHD-free relapse-free survival (GRSF)(hazard ratio [HR]=0.9, 95% confidence interval [CI]: 0.8-1.1, *P*=0.5) and overall survival (HR=1.0, 95% CI: 0.8-1.2, *P*=0.8). They had however, a lower incidence of chronic GvHD (cGvHD) (HR=0.7, 95% CI: 0.6-0.9, *P*=0.01). In the cohort of patients receiving grafts from HLA-matched unrelated donor, patients given PBSC with ATG (n=2,318) had better severe GvHD-free and relapse-free survival (GRFS) than those given BM without ATG (n=303) (HR=0.8, 95% CI: 0.6-0.9, *P*=0.001). They also had a lower incidence of cGvHD (HR=0.6, 95% CI: 0.5-0.8, *P*=0.0006) and better overall survival (HR=0.8, 95% CI: 0.6-1.0, *P*=0.04). In summary, these data suggest that PBSC with ATG results in comparable (in the case of sibling donor) or significantly better (in the case of unrelated donor) severe GRFS than BM without ATG in patients with AML in complete remission receiving grafts after myeloablative conditioning.

Introduction

A number of phase III trials have compared peripheral blood stem cells (PBSC) with bone marrow (BM) as the stem cell source for allogeneic hematopoietic cell transplantation in patients given grafts after myeloablative regimens.[1,2] A meta-analysis of trials performed in patients given grafts from human leukocyte antigen (HLA)-matched sibling donors (MSD) revealed that the use PBSC of instead of BM was associated with a higher incidence of grade III-IV acute graft-*versus*-host dis-

ease (aGvHD) and (extensive) cGvHD, as well as a lower incidence of relapse (IR) and better overall survival (OS) in the subgroup of patients with late-stage disease.[3] Further, the only phase III trial performed in patients given grafts from HLA-matched unrelated donors (MUD) showed that patients randomized to the BM group had a lower inci-
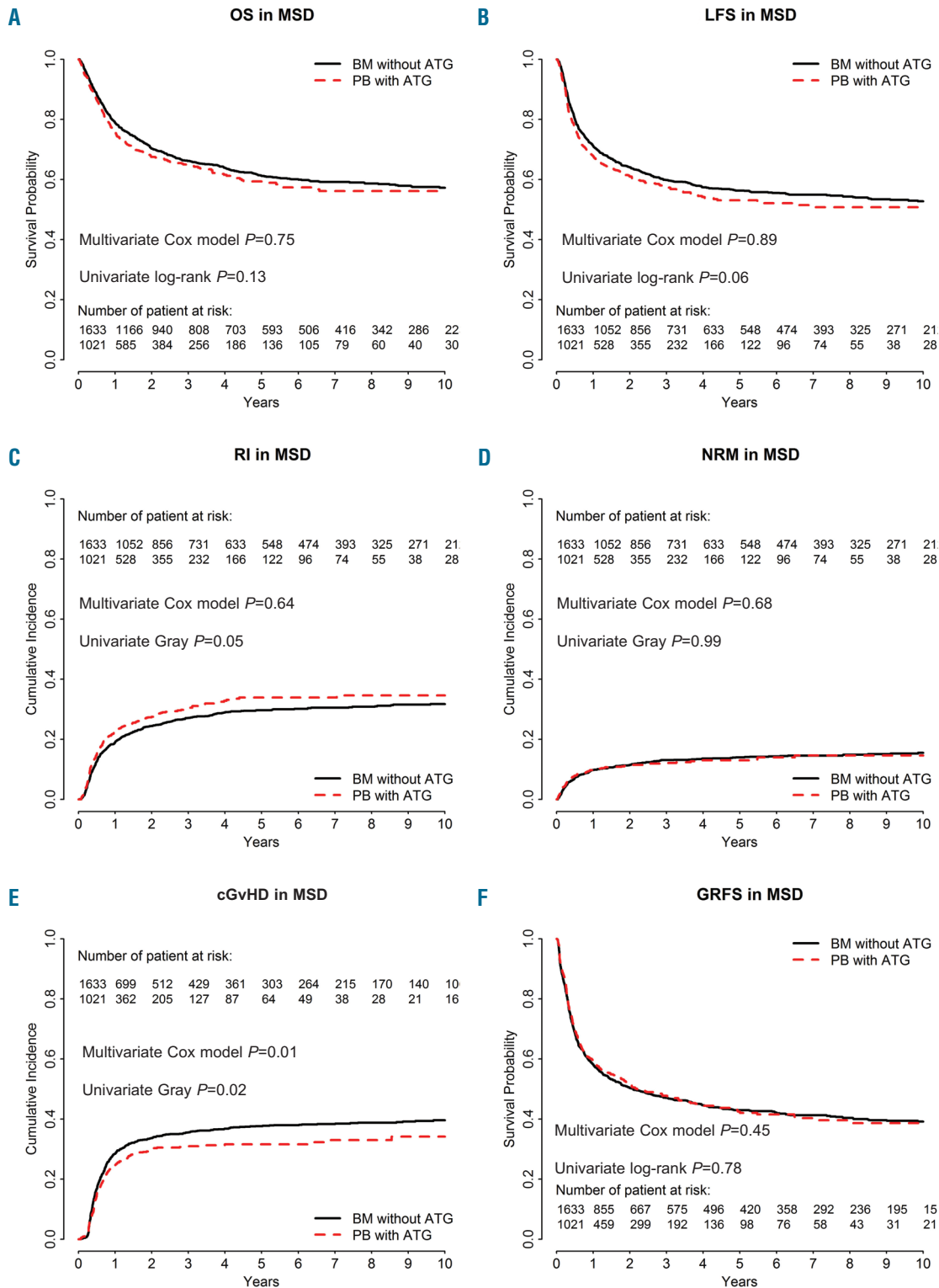
Figure 1. Comparison of outcomes in bone marrow (BM) patients without anti-thymocyte globulin (ATG) and in those given peripheral blood (PB) stem cells with ATG (the dotted line shows the PBSC with ATG curve adjusted for relevant covariates) in the cohort of patients receiving grafts from HLA-identical sibling donor (MSD). (A) Overall survival (OS), $P=0.13$. (B) Leukemia-free survival (LFS), $P=0.065$. (C) Incidence of relapse (RI), $P=0.0496$. (D) Non-relapse mortality (NRM), $P=0.989$. (E) chronic graft-*versus*-host disease (cGvHD), $P=0.0186$. (F) GvHD-free and relapse-free survival (GRFS), $P=0.782$.

dence of cGvHD, similar OS, and better patient-reported outcomes at 5 years after transplantation than those randomized to the PBSC arm.[4,5] This might suggest that, at least in the MUD setting, BM may be preferred over PBSC as a stem cell source in patients receiving grafts after myeloablative regimens. In concordance with these findings, a recent European Group for Blood and Marrow Transplantation (EBMT) study observed a better GvHD-free relapse-free survival (GRFS) with BM than with peripheral blood (PB) as the stem cell source.[6]

In the last two decades, five phase III trials have assessed the impact of anti-thymocyte globulins (ATG) on transplantation outcomes in patients given grafts (mainly PBSC) from MSD (n=1)[7] or MUD (n=4).[8-11] These five trials demonstrated a lower incidence of cGvHD with ATG.[12] Two of three trials assessing the impact of ATG on GRFS[13] observed better GRFS in patients randomized to ATG,[7,10] while the study by Soiffer *et al.* failed to demonstrate this effect.[11] ATG was also found to improve GRFS in a registry study including data from patients given grafts from HLA-identical siblings after myeloablative fludarabine + busulfan regimens.[13]

These findings prompted us to compare transplantation outcomes in AML patients following BMT without ATG *versus* PBSC transplantation with ATG in the first or second complete remission (CR).

Methods

Ethics

The scientific board of the Acute Leukaemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) approved this research project. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines.

Inclusion/exclusion criteria and study endpoints

Inclusion criteria included adult patients, *de novo* or secondary AML, myeloablative conditioning, MSD or 10/10 HLA-matched unrelated donors (MUD), first or second CR, first allo-transplantation from 2000 to 2017 at an EBMT-affiliated center, and either BM without ATG, or PBSC with ATG. Exclusion criteria consisted of *in vitro* T-cell depletion of the graft, and prior administration of alemtuzumab. The primary endpoint was GRFS. Secondary endpoints included grade II-IV GvHD, RI, nonrelapse mortality (NRM), leukemia-free survival (LFS) and OS.

Statistical analyses

Myeloablative conditioning was defined as use of ≥ 6 Gy TBI, busulfan > 8 mg/kg, or melphalan > 140 mg/m^2 as previously reported.[14] The cytogenetic AML risk was determined as previously reported.[15,16]

NRM was defined as death without prior or current disease recurrence. Events in the composite endpoint GRFS included grade III-IV aGvHD, extensive cGvHD, relapse or death as previously reported.[17]

OS, LFS and GRFS were estimated using the Kaplan-Meier estimates. Cumulative incidence functions (CIF) were used for RI and NRM in a competing risk setting, since death and relapse are competing together. In estimating the cumulative incidence of aGvHD and cGvHD, we considered relapse and death to be competing events. Univariate analyses were done using Gray's test for CIF and the log-rank test for GRFS, OS and LFS. Since there were some imbalances between the groups we performed multivariate Cox models to further determine the impact of the

graft type on transplantation outcome. These Cox models were adjusted for disease status at transplantation, female donor to male recipient or not, CMV serostatus, use or not of total body irradiation (TBI), year of transplantation, age at transplantation, primary *versus* secondary AML, and cytogenetic risk. In order to take into account the center effect, we introduced a frailty for each center into the model, as previously reported.[18,19] Specifically, we introduced a random effect (also named frailty effect) in the Cox multivariate models. Then, the same random effect was shared by all patients within the same center. In order to assess whether there was a statistical interaction between the year of transplantation and the association between BMT without ATG *versus* PBSC with ATG and the incidence of relapse, we introduced the interaction term between cell source and year as a binary variable (with the median year by group as the cut-off) in the Cox multivariate model for relapse. Results are presented as hazard ratios (HR) and 95% confidence intervals (95% CI). The HR for year of transplantation corresponded to a 5-year increase and to a 10-year increase for the age at transplantation. As planned in the synopsis, the analyses were done separately for MSD and MUD. The interaction between graft type (i.e. BM without ATG or PBSC with ATG) and donor type (MSD *versus* MUD) was confirmed for several outcomes (*data not shown*).

Results

BM without ATG *versus* PBSC with ATG in MSD recipients

Patients

A total of 2,654 MSD recipients met the inclusion/exclusion criteria, comprising 1,633 BM without ATG patients and 1,021 PBSC with ATG patients (Table 1). In comparison to BM without ATG recipients, PBSC with ATG patients were older (median 48 years *vs.* 40 years old), were transplanted more recently (median year of transplantation 2014 *vs.* 2008), less likely to have a good cytogenetic risk (10% *vs.* 16%), more likely to have secondary AML (11% *vs.* 6%), less frequently received TBI in the conditioning regimen (12% *vs.* 32%), and were more frequently male patients receiving grafts from female donors (25% *vs.* 22%).

GvHD

The 100-day incidence of grade 2-4 aGvHD was 27% (95% CI: 25-29%) in BM without ATG recipients *versus* 18% (95% CI: 16-20%) in PBSC with ATG patients (*P*<0.001). For grades III-IV, the figures were 9% (95% CI: 8-11%) and 6% (95% CI: 4-7%), respectively (*P*=0.002). In multivariate analyses, the difference for grade II-IV aGvHD between PBSC with ATG *versus* BM without ATG was no longer statistically significant (HR=0.8, 95% CI: 0.7-1.1, *P*=0.12) (Table 2) while the use of TBI in the conditioning was associated with a higher incidence of grade II-IV aGvHD (HR=1.4, 95% C1: 1.1-1.8, *P*=0.004). In contrast, a more recent transplantation year was associated with a lower incidence of grade II-IV aGvHD (HR=0.8, 95% CI: 0.7-0.9, *P*=0.0004).

At 2 years the CI of cGvHD was 34% (95% CI: 31-36%) in BM without ATG recipients *versus* 30% (95% CI: 27-33%) in PBSC with ATG patients (*P*=0.02) (Figure 1E). This association remained statistically significant on multivariate analysis with a lower risk of cGvHD among PBSC with ATG recipients (HR=0.7, 95% CI: 0.6-0.9,

P=0.01). In contrast, female donor to male recipient (HR=1.5, 95% C1: 1.3-1.7, *P*<0.001), and older age at transplantation (HR=1.07, 95% C1: 1.0-1.14, *P*=0.049) were associated with a higher incidence of cGvHD.

Relapse and non-relapse mortality

The 2-year CI of relapse was 25% (95% CI: 22-27%) in BM without ATG recipients *versus* 28% (95% CI: 25-31%) in PBSC with ATG patients (*P*=0.0496) (Figure 1C). After

Table 1. Patient characteristics among human leucocyte antigen-identical sibling donor (MSD) recipients

Variable	BM without ATG (n=1633)	PBSC with ATG (n=1021)	P
Follow up, median (95% CI)	6.1 (5.9-6.5)	2.3 (2.1-2.5)	
Age of patient at HSCT (years), Median (IQR)	40 (30-48)	48 (38-56)	<0.0001
Sex, n (%)			0.04
Male	794 (49)	535 (53)	
Female	838 (51)	480 (47)	
Missing	1	6	
Karnofsky, n (%)			
<80	30 (2)	29 (3)	0.33
≥80	1270 (98)	950 (97)	
Missing	333	42	
Status at transplant, n (%)			
CR1	1407 (86)	893 (87)	0.34
CR2	226 (14)	128 (13)	
Cytogenetic risk			<0.0001
Good[1]	190 (16)	62 (10)	
Intermediate[2]	804 (70)	428 (68)	
Poor[3]	158 (14)	136 (22)	
Missing	481	395	
AML type			<0.0001
Primary	1537 (94)	908 (89)	
Secondary	96 (6)	113 (11)	
Year of transplant, Median (IQR)	2008 (2004-2012)	2014 (2011-2016)	<0.0001
Sex mismatch, n (%)			0.03
Female to male	355 (22)	257 (25)	
CMV donor/patient, n (%)			0.004
-/-	356 (24)	187 (19)	
+/-	137 (9)	103 (10)	
-/+	247 (17)	140 (14)	
+/+	753 (50)	555 (56)	
Missing	140	36	
Conditioning, n (%)			<0.0001
Chemotherapy-based MAC[4]	1118 (68)	896 (88)	
TBI-based MAC	515 (32)	125 (12)	
Post-grafting immunosuppression, n (%)			
CNI + MTX	1472 (90)	523 (51)	
CNI + MMF	58 (4)	193 (19)	
CNI alone	46 (3)	218 (21)	
Other/missing	57 (3)	87 (9)	
ATG, n (%)			
Thymoglobuline	–	249 (30)	
Median (IQR) dose, mg/kg		5.0 (5.0-5.6)	
ATG-Fresenius	–	569 (70)	
Median (IQR) dose, mg/kg		30 (30-35)	
Missing	–	203	

HLA: human leucocyte antigen; MSD: HLA-identical sibling donor; BM: bone marrow; PBSC: peripheral blood stem cells; CI: confidence interval; ATG: anti-thymocyte globulin; AML: acute myeloid leukemia; HSCT: hematopoietic stem cell transplantation; IQR: interquartile ranges; CR: complete remission; CMV: cytomegalovirus; MAC: myeloablative conditioning; TBI: total body irradiation; CNI: calcineurin inhibitor; MTX: methotrexate; MMF: mycophenolate mofetil;[1]defined as t(8;21), t(15;17), inv or del (16), or acute promyelocytic leukemia, these abnormalities only or combined with others; [2]defined as all cytogenetics not belonging to the good or high risk (including trisomies); [3]defined as 11q23 abnormalities, complex karyotype, abnormalities of chromosomes 5 and 7; [4]defined as use of ≥ 6 Gy TBI, busulfan > 8 mg/kg, or melphalan > 140 mg/m^2.

adjusting for potential confounding factors by multivariate analyses there was no significant impact of the graft type on relapse (HR=1.0, 95% CI: 0.8-1.2, P=0.6). In contrast, a more recent year of transplantation (HR=1.1, 95% C1: 1.0-1.2, P=0.02) was associated with a higher risk of relapse. There was no interaction between the association of graft type and the risk of relapse and year of transplantation (interaction test P=0.38). Unadjusted comparison of relapse incidence between the two groups *per* 6-year periods is shown in the *Online Supplementary Table S2*. We fur-
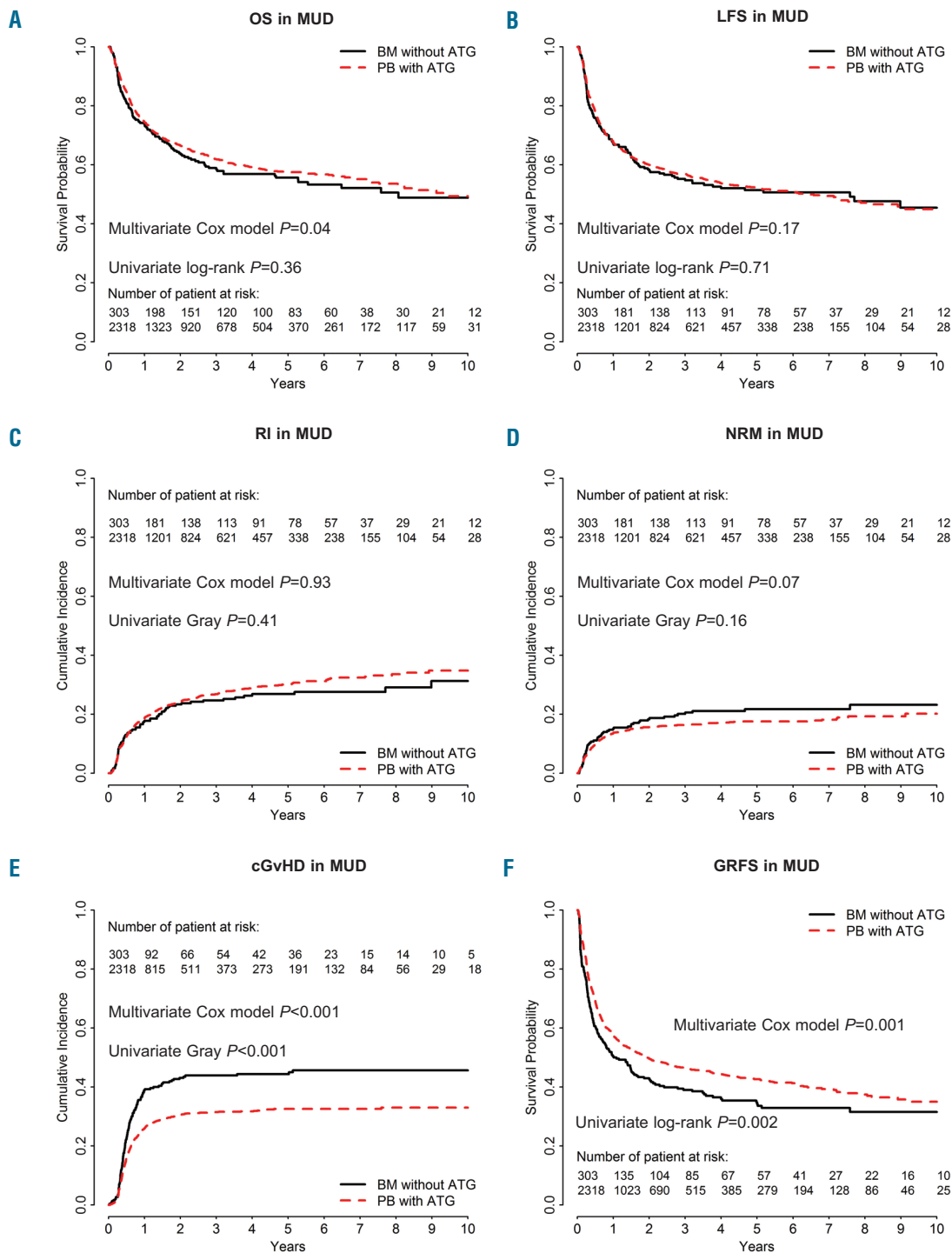
Figure 2. Comparison of outcomes in bone marrow (BM) patients without anti-thymocyte globulin (ATG)and in those given peripheral blood (PB) stem cells with ATG (the dotted line shows the PBSC with ATG curve adjusted for relevant covariates) in the cohort of patients receiving grafts from 10/10 HLA-matched unrelated donors (MUD). (A) Overall survival (OS), *P*=0.36. (B) Leukemia-free survival (LFS), P=0.71. (C) Incidence of relapse (RI), *P*=0.41.(D) Non-relapse mortality (NRM), *P*=0.16. (E) Chronic graft-*versus*-host disease (cGvHD), *P*<0.001. (F) GvHD-free and relapse-free survival (GRFS), *P*=0.002.

ther investigated whether there was a statistical interaction between the use of TBI in the conditioning regimen and the impact of graft type on relapse risk. Among patients given graft from MSD, there was no such interaction (*P*-value for the interaction test = 0.97).

The 2-year CI of NRM was 11.5% in both groups (Figure 1D). In multivariate analyses, PBSC with ATG was associated with a similar risk of NRM to BM (HR=1.1, 95% CI: 0.8-1.4, P=0.7). In contrast, older age at transplantation (HR=1.5, 95% CI: 1.4-1.7, *P*<0.001) and secondary *versus de novo* AML (HR=1.5, 95% CI: 1.0-2.1, *P*=0.03) were associated with a higher NRM while a more recent year of transplantation was associated with a lower NRM (HR=0.7, 95% C1: 0.6-0.8, *P*<0.001).

OS and LFS

The 2-year OS and LFS were 70% (95% CI: 68-73%) and 64% (95% CI: 62-66%) in BMT without ATG patients *versus* 68% (95% CI: 64-71%, P=0.1) and 61% (95% CI: 58-64%, P=0.06) in PBSC with ATG patients, respectively (Figure 1A-B). After adjusting for potential confounding factors by multivariate analyses, the use of PBSC with ATG was no different to BM with respect to OS (HR=1.0, 95% CI: 0.8-1.2, *P*=0.8) and LFS (HR=1.0, 95% CI: 0.8-1.2, *P*=0.9). In contrast, second CR at transplantation (HR=1.3, 95% CI: 1.0-1.5, *P*=0.03), and older patient age (HR=1.2, 95% CI: 1.1-1.3, *P*<0.001) were associated with worse OS. The same factors were also significantly associated with worse LFS: second CR at transplantation (HR=1.2, 95% CI: 1.0-1.5; *P*=0.04), and older patient age (HR=1.2, 95% CI: 1.1-1.2, *P*<0.001).

GRFS

At 2 years, GRFS was 50% (95% CI: 48-53%) in BMT without ATG patients *versus* 52% (95% CI: 48-55%) in the PBSC with ATG group (*P*=0.8) (Figure 1F). This was confirmed on multivariate analysis including data from all patients (HR=0.9, 95% CI: 0.8-1.1, *P*=0.5) as well as in further sensitivity analysis restricted to patients given a combination of a calcineurin inhibitor and methotrexate as GvHD prophylaxis (HR=1.0, 95% CI: 0.8-1.2, *P*=0.9). In contrast, female donor to male recipient (HR=1.2, 95% CI: 1.0-1.3, *P*=0.01), and older patient age (HR=1.1, 95% CI: 1.1-1.1, *P*<0.001) were associated with a worse GRFS.

BM without ATG *versus* PBSC with ATG in MUD recipients
Patients

A total of 2,621 recipients met the inclusion/exclusion criteria. Comprising 303 patients in the BM group and 2,318 in the PBSC with ATG group (Table 3). In comparison to BM recipients, PBSC with ATG patients were older (median 48 years *vs.* 42 years old), were transplanted more recently (median year of transplantation 2013 *versus* 2012) and were more frequently transplanted in the first CR (79% *vs.* 71%).

GvHD

The 100-day incidence of grade II-IV aGvHD was 44% in BMT without ATG recipients *vs.* 24% in PBSC with ATG recipients (*P*<0.0001). For grade 3-4, the figures were 17% (95% CI: 13-21%) and 7% (95% CI: 6-8%), respectively (*P*<0.001). In multivariate analysis, PBSC with ATG patients had a significantly lower incidence of grade II-IV aGvHD than BM recipients (HR=0.5, 95% CI: 0.4-0.7;

P<0.001). No other factor was significantly associated with grade II-IV aGvHD in multivariate analysis (*Online Supplementary Table S4*).

The 2-year CI of cGvHD was 43% (95% CI: 37-49%) in BM without ATG recipients *versus* 30% (95% CI: 28-32%) in PBSC with ATG patients (*P*<0.0001) (Figure 2E). On multivariate analysis, PBSC with ATG, in comparison to BM without ATG, was associated with a lower incidence of cGvHD (HR=0.6, 95% CI: 0.5-0.8, *P*=0.0006) (Table 2), but no other factor was significantly associated with cGvHD.

Relapse and non-relapse mortality

The 2-year CI of relapse was 23% (95% CI: 19-29%) in BMT without ATG recipients *versus* 24% (95% CI: 23-26%) in PBSC with ATG patients (*P*=0.4) (Figure 2C). On multivariate analysis, as observed in the MSD cohort, there was no significant impact of the graft type on relapse (HR=1.0, 95% CI: 0.8-1.3, *P*=0.9), but a more recent transplantation was significantly associated with a higher risk of relapse (HR=1.2, 95% CI: 1.0-1.4, *P*=0.03) (*Online Supplementary Table S1*). There was no interaction between the association of graft type and the risk of relapse and year of transplantation (interaction test *P*=0.13). Unadjusted comparison of relapse incidence between the two groups per 6-year periods is shown in the *Online Supplementalry Table S2*. We further investigated whether there was a statistical interaction between the use of TBI in the conditioning regimen and the impact of the graft type on the relapse risk. Among patients given graft from MUD, there was such an interaction (*P*-value for the interaction test=0.05). Specifically, in the subgroup of patients given TBI-based

Table 2. Outcomes (multivariate Cox models).

Outcomes	HR (95% CI) PBSC with ATG vs BMT without ATG	P value[1]
MSD		
Grade II-IV acute GvHD	0.82 (0.64-1.05)	0.12
Chronic GvHD	0.74 (0.59-0.93)	0.01
Relapse incidence	0.96 (0.79-1.16)	0.64
Non relapse mortality	1.07 (0.79-1.44)	0.68
Leukemia-free survival	0.99 (0.84-1.16)	0.89
Overall survival	0.97 (0.81-1.16)	0.75
GvHD-free and relapse-free survival	0.94 (0.81-1.1)	0.45
MUD		
Grade 2-4 acute GvHD	0.54 (0.41-0.71)	<0.001
Chronic GvHD	0.62 (0.47-0.81)	<0.001
Relapse incidence	0.99 (0.77-1.27)	0.93
Non relapse mortality	0.72 (0.50-1.02)	0.07
Leukemia-free survival	0.87 (0.72-1.06)	0.17
Overall survival	0.80 (0.65-0.99)	0.04
GvHD-free and relapse-free survival[2]	0.76 (0.64-0.90)	0.001

HLA: human leucocyte antigen; MSD: HLA-identical sibling donor; MUD: 10/10 HLA-matched unrelated donors; HR: hazard ratio; CI: confidence interval; BM: bone marrow; BMT: bone marrow transplant; PBSC: peripheral blood stem cells; ATG: anti-thymocyte globulin; GvHD: graft-*versus*-host disease.[1]Factors included in the models are: disease status at transplantation, female donor to male recipient or not, cytomegalovirus (CMV) serostatus, use or not of total body irradiation (TBI), year of transplantation, age at transplantation, primary *versus* secondary acute myeloid leukemia (AML), cytogenetic risk and frailty center effect; [2]defined as no death, no relapse, no grade III-IV acute GvHD and no extensive chronic GvHD.

conditioning we observed a lower risk of relapse in PBSC with ATG patients than in BMT without ATG patients (HR=0.56, 95% CI: 0.39-0.81, *P*=0.002) while this was not the case in patients given chemotherapy-based conditioning (HR=0.94, 95% CI: 0.70-1.26, *P*=0.68).

The 2-year CI of non-relapse mortality was 18% in BMT without ATG patients *versus* 16% in PBSC with ATG patients (*P*=0.16) (Figure 2D). On multivariate analysis, there was a non-significant trend for lower NRM in PBSC with ATG patients (HR=0.7, 95% CI: 0.7-

Table 3. Patient characteristics among 10/10 human leucocyte antigen-matched unrelated donor recipients.

Variable	BM without ATG (n=303)	PBSC with ATG (n=2318)	*P*
Follow up, median (95% CI)	5.0 (4.0-5.4)	2.7 (2.5-3.0)	
Age of patient at HSCT (years), Median (IQR)	42 (31-50)	48 (37-56)	<0.001
Sex, n (%)			0.50
Male	152 (50)	1210 (52)	
Female	151 (50)	1108 (48)	
Missing	0	0	
Karnofsky, n (%)			0,99
<80	6 (2)	46 (2)	
≥80	283 (98)	2156 (98)	
Missing	14	116	
Status at transplant, n (%)			
CR1	215 (71)	1836 (79)	0.001
CR2	88 (29)	482 (21)	
Cytogenetic risk			0.94
Good[1]	30 (14)	176 (14)	
Intermediate[2]	137 (65)	793 (64)	
Poor[3]	43 (21)	266 (22)	
Missing	93	1083	
AML type			0.014
Primary	277 (91)	2002 (86)	
Secondary	26 (9)	316 (14)	
Year of transplant, Median (IQR)	2012 (2009-2014)	2013 (2011-2015)	<0.001
Sex mismatch, n (%)			
Female to male	28 (9)	279 (12)	0.15
CMV donor/patient, n (%)			0.09
-/-	99 (34)	608 (27)	
+/-	27 (9)	179 (8)	
-/+	84 (28)	703 (32)	
+/+	85 (29)	741 (33)	
Missing	8	87	
Conditioning, n (%)			<0.001
Chemotherapy -based MAC[4]	189 (62)	1873 (81)	
TBI-based MAC	114 (38)	445 (19)	
Post-grafting immunosuppression, n (%)			
CNI + MTX	262 (86)	1468 (63)	
CNI + MMF	17 (6)	556 (24)	
CNI alone	8 (3)	134 (6)	
Other/missing	16 (5)	160 (7)	
ATG, n (%)			
Thymoglobuline	–	736 (42)	
Median (IQR) dose, mg/kg		5.5 (5.0-6.0)	
ATG-Fresenius	–	1013 (58)	
Median (IQR) dose, mg/kg		40 (30-60)	
Missing	–	569	

HLA: human leucocyte antigen; MUD: 10/10 HLA-matched unrelated donors; CI: confidence interval; BM: bone marrow; PBSC: peripheral blood stem cells; AML: acute myeloid leukemia; ATG: anti-thymocyte globulin; HSCT: hematopoietic stem cell transplantation; IQR: interquartile range; CR: complete remission; CMV: cytomegalovirus; MAC: myeloablative conditioning; TBI: total body irradiation; CNI: calcineurin inhibitor; MTX: methotrexate; MMF: mycophenolate mofetil;[1]defined as t(8;21), t(15;17), inv or del (16), or acute promyelocyticleukemia, these abnormalities only or combined with others; [2]defined as all cytogenetics not belonging to the good or high risk (including trisomies); [3]defined as 11q23 abnormalities, complex karyotype, abnormalities of chromosomes 5 and 7, as well as 3q26 and 17p abnormalities, as defined previously16; [4]defined as use of ≥ 6 Gy TBI, busulfan > 8 mg/kg, or melphalan > 140 mg/m^{2}.

1.0, *P*=0.07). Factors associated with NRM on multivariate analysis included older age at transplantation (HR=1.4, 95% CI: 1.3-1.5, *P*<0.001) and secondary AML (HR=1.4, 95% CI: 1.1-1.9, *P*=0.01) while a more recent transplant year was associated with lower NRM (HR=0.8, 95% CI: 0.7-1.0, *P*=0.03).

OS and LFS

The 2-year OS and LFS were 64% (95% CI: 58-70%) and 58% (95% CI: 53-64%) in BMT without ATG patients *versus* 67% (95% CI: 64-69%, *P*=0.3) and 60% (95% CI: 58-62%, *P*=0.7) in PBSC with ATG patients, respectively (Figure 2A-B). After adjusting for potential confounding factors, the use of PBSC with ATG was associated with a better OS (HR=0.8, 95% CI: 0.6-1.0, *P*=0.04) than with BM, but there was no significant difference in LFS between the groups (HR=0.9, 95% CI: 0.7-1.1, *P*=0.2). As well as being in the BMT group, older age was significantly associated with a poorer OS (HR=1.2, 95% CI: 1.1-1.3, *P*<0.0001) and a worse LFS (HR=1.1, 95% CI: 1.1-1.2, *P*<0.0001).

Causes of death were comparable in both groups expect for a higher frequency of infectious-related death in the PBSC with ATG group (23% *vs.* 11%) (*Online Supplementary Table S3*).

GRFS

The 2-year GRFS was 43% (95% CI: 37-49%) *versus* 50% (95% CI: 47-52%) in BMT without ATG and PBSC with ATG recipients, respectively (*P*=0.002) (Figure 2F). This was confirmed in multivariate analysis including data from all patients (HR=0.8, 95% CI: 0.6-0.9, *P*=0.001) as well as in further sensitivity analysis restricted to patients given a combination of a calcineurin inhibitor and methotrexate as GvHD prophylaxis (HR=0.8, 95% CI: 0.6-0.9, *P*=0.01). Finally, older patient age was also associated with worse GRFS (HR=1.1, 95% CI: 1.0-1.1, *P*=0.004) in the whole cohort of patients.

Discussion

Several studies have now established that the use of PBSC (without ATG) instead of BM is associated with a high incidence of (severe) cGvHD affecting the long-term well-being of the patients.[2,5] In contrast, several phase III trials have demonstrated a beneficial impact of ATG on cGvHD.[12] Here, we compare the outcomes of AML patients given BMT without ATG *versus* PBSC with ATG, in the setting of AML in first or second CR. We elected to restrict the analyses of patients given grafts after myeloablative conditioning since it was a inclusion criteria in most phase III ATG studies, although many AML patients are nowadays transplanted following reduced-toxicity regimens.[20,21] Several observations can be made.

First, the use of PBSC with ATG was associated with a lower incidence of cGvHD both in the MSD and MUD datasets. This clearly demonstrates that ATG administration is able to counterbalance the high risk of cGvHD associated with the use of PBSC (instead of BMT without ATG).

Importantly, the incidence of relapse was not significantly different in BMT without ATG and in PBSC with ATG patients in both datasets. This may appear surprising given the tight association between cGvHD and graft-*versus*-leukemia effects, and is consistent with most phase III ATG trials showing,[22-24] a reduction of cGvHD without an increase in the relapse risk.[12] Similar findings were observed in the RIC setting in a large registry study.[25]

Given the data of the Soiffer *et al*. phase III study showing detrimental effects of ATG in patients given TBI-based conditioning regimen,[11] we investigated whether, in our study, there was a statistical interaction between graft type and the risk of relapse and the use of TBI in the conditioning regimen. Interestingly, we observed a lower risk of relapse only in the subgroup of patients given TBI-based conditioning suggesting no adverse effects of ATG in patients given TBI-based conditioning. These data are in concordance with recent observations reported by our group.[26]

The main endpoint of our retrospective study was GRFS, a relatively new composite endpoint which aims at capturing the rate of cure without ongoing transplant-related morbidity.[27] We observed a non-significant difference in GRFS with the two strategies in the cohort of patients given grafts from MSD, and a significantly better GRFS with PBSC with ATG in the cohort of patients given grafts from MUD. We thus advocate that our data might support the use of PBSC with ATG rather than BMT without ATG, in AML patients in CR at transplantation.

An interesting finding of our study was an increasing relapse incidence (but decreasing non relapse mortality incidence) with more recent transplantations. This might be due to a higher proportion at high risk of relapse (as example more patient with persistent minimal residual disease at transplantation) in more recent years of transplantation. Unfortunately, we do not have data on the MRD status at transplantation for many patients included in this survey.

There are some limitations of the study such as its design (it is however unlikely that a prospective randomized phase III trial will address this question in the near future), the lack of data on mutational AML landscape and minimal residual disease, a high proportion of missing cytogenetic data, the lack of ATG dose data for several patients, and some imbalances between the groups. However these imbalances were adjusted for in the multivariate Cox models. The strengths of the study are the number of patients in each group and their relative uniformity (one single disease, all patients in first or second CR at transplantation, no HLA-mismatches, only myeloablative conditioning regimen).

In conclusion, our data suggest that PBSC transplantation with ATG results in comparable (in case of MSD) or significantly better (in case of MUD) GRFS than BMT without ATG in patients with AML in CR receiving grafts after myeloablative conditioning. These data might support the use of PBSC with ATG compared to BMT without ATG in patients receiving grafts from MSD or MUD after myeloablative conditioning as treatment for AML in CR.

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