SUPPLEMENTARY APPENDIX

Pre-transplant prognostic factors of long-term survival after allogeneic peripheral blood stem cell transplantation with matched related/unrelated donors

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ONLINE SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

Pretransplant comorbidity assessment

As pre-transplant pulmonary function tests were not systematically performed before 2006 in our institution, the HCT-CI was assessable only for patients who underwent PB-HSCT between January 2006 and December 2010.

Transplant modalities and outcomes: definitions

Myeloablative conditioning (MAC) regimens included either high dose busulfan (dose > 8 mg/kg orally or intravenous equivalent) or high dose total body irradiation (≥8Gy fractioned dose), both associated with cyclophosphamide. Regimens not meeting these criteria were classified as reduced intensity conditioning (RIC). A count of $4.5x10^6$ CD34+ cells/kg recipient's weight was defined as the cut-off for low and high CD34+ cell dose, based on institutional guidelines and previous studies[40].

OS was defined as the time from HSCT to death from any cause. PFS was considered as the time from HSCT to disease relapse or progression or death from any cause, whichever occurred first. Relapse was defined as recurrence of the original malignancy. NRM was considered as death from any cause in patients who did not relapse. Chronic GVHD was diagnosed according to the 2005 NIH Consensus Criteria.

Statistical methods: variables

Tested variables in univariate analysis included (only pre-transplant parameters): donor type (MRD vs. MUD), patient age at transplant, DRI, donor age, donor/recipient gender match (female donor/ male recipient vs. other combinations), donor/recipient CMV sero-status match, donor/recipient ABO blood groups match, graft CD34+ cell dose, graft CD3+ cell dose, conditioning regimen intensity (MAC vs. RIC) and use of antithymocyte globulin (ATG) as part of conditioning regimen or for GVHD prophylaxis. Because a donor age ≥ 60 years appeared to be associated with survival in univariate analysis and because 60 years was the usual upper age limit for MUD, we further defined 3 groups of donors according to type and age: MUD, MRD younger than 60 years (MRD<60y) and MRD aged 60 years or older (MRD ≥60y). We used the new defined variable (donor type/age group) in the multivariate setting.

Concerning OS and PFS, because evidence of non-proportional hazards according to time from HSCT for donor type/age groups (MRD ≥60y : P=0.003 and P=0.014 for OS and PFS, respectively), we performed a time-dependent effects analysis for this variable by assessing hazards during four successive quartiles of time, each corresponding to a period during which 25% of deaths had occurred within the entire cohort (0 to 6, 6 to 9, 9 to 18 and ≥ 18 months after PB-HSCT).

SUPPLEMENTAL TABLES

Table S1. Univariate analysis of prognostic value of pre-transplant factors on outcomes after PB-HSCT. Hazard ratio (HR) and P-value are shown.

	Overall mortality (inverse of OS)		**Treatment failure (inverse of PFS)**		**Relapse**		**NRM**		**Chronic GVHD**	
Pre-transplant variable	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Donor type										
MUD	1		1		1		1		1	
MRD	0.90	0.49	1.05	0.72	1.51	**0.039**	0.69	**0.072**	0.84	**0.22**
Recipient age, years										
< 20	0.80	0.62	0.87	0.73	0.85	0.73	0.93	0.91	0.91	0.78
20 – 29	1		1		1		1		1	
30 – 39	1.35	0.33	1.20	0.51	1.08	0.84	1.48	0.42	1.24	0.41
40 – 49	1.37	0.26	1.29	0.32	0.95	0.87	2.00	**0.10**	0.94	0.78
50 – 59	1.38	**0.23**	1.26	0.34	1.03	0.92	1.74	**0.18**	0.98	0.94
≥ 60	2.03	**0.024**	1.53	0.26	1.17	0.68	2.31	**0.079**	0.95	0.87
DRI										
Low	1.01	0.97	0.91	0.65	0.46	**0.028**	1.62	**0.068**	1.17	0.41
Intermediate	1		1		1		1		1	
High	1.41	**0.055**	1.32	**0.093**	1.19	0.42	1.53	**0.096**	1.21	0.28
Very high	2.90	**0.004**	2.29	**0.017**	2.55	**0.027**	1.91	0.28	1.02	0.97
Conditioning regimen										
MAC	1		1		1		1		1	
RIC	0.82	0.26	1.01	0.96	1.29	**0.21**	0.75	**0.18**	0. 93	0.63
ATG										
No	1		1		1		1		1	
Yes	1.07	0.74	1.25	**0.20**	1.55	**0.042**	0.89	0.70	0.73	**0.095**
CD34+ cell dose (x 10^6/kg)										
≤ 4.5	1		1		1		1		1	
> 4.5	0.62	**0.007**	0.70	**0.032**	0.82	0.41	0.58	**0.022**	1.02	0.91
CD3+ cell dose, x 10^8/kg										
< 2	1		1		1		1		1	
2 - 3	0.74	**0.085**	0.78	**0.11**	0.90	0.62	0.64	**0.068**	1.17	0.37
> 3	0.61	**0.007**	0.64	**0.008**	0.67	**0.078**	0.61	**0.043**	1.18	0.32
Donor age, years										
<30	1		1		1		1		1	
30-39	0.82	0.35	0.98	0.91	1.06	0.83	0.88	0.67	0.83	0.34
40-49	0.99	0.96	1.11	0.60	1.08	0.76	1.14	0.66	0.94	0.74
50-59	1.14	0.57	1.07	0.75	1.00	0.99	1.15	0.65	1.18	0.41
≥60	1.90	**0.012**	1.69	**0.033**	2.09	**0.018**	1.22	0.62	0.56	**0.074**
Female donor/male recipient										
No	1		1		1		1		1	
Yes	1.12	0.49	1.00	0.99	0.94	0.77	1.07	0.76	1.39	**0.025**
Donor/recipient CMV status										
Negative/Negative	1		1		1		1		1	
Negative/Positive	0.95	0.82	1.03	0.86	0.94	0.82	1.14	0.62	1.10	0.60
Positive/Negative	0.69	**0.15**	0.76	0.25	0.77	0.41	0.75	0.42	1.15	0.51
Positive/Positive	1.06	0.75	1.10	0.59	1.22	0.37	0.95	0.83	1.02	0.91
Donor/recipient ABO match										
Compatibility	1		1		1		1		1	
Major incompatibility	0.95	0.78	0.91	0.58	0.89	0.58	0.95	0.84	0.85	0.32
Minor incompatibility	0.97	0.89	0.82	0.28	0.64	**0.094**	1.07	0.79	0.88	0.48

ATG indicates antithymocyte globulin; CMV, cytomegalovirus; DRI, disease risk index; GVHD, graft-versus-host disease; MAC, myeloablative conditioning; MRD, matched related donor; MUD, matched unrelated donor; NRM, non relapse mortality; OS, overall survival; PFS, progression free survival; RIC, reduced-intensity conditioning.

Table S2. Baseline characteristics of patients transplanted with MRD≥60y

Pre-transplant variable	N= 36 no.
Recipient age, median (range) years	58 (25 to 67)
20 – 29	1
40 – 49	5
50 – 59	19
≥60	11
Male gender	24
Disease	
AML	11
MDS	12
MPN	4
CLL	5
MM	4
DRI	
Low	5
Intermediate	16
High	11
Very High	4
aDRI	
Low	6
Intermediate	16
High	8
Very High	6
Conditioning regimen	
MAC	9
RIC	27
ATG	9
Graft CD34+ cell dose, $x10^6$/kg Median, range	5.8 (1.2 to 12.9)
< 4.5	11
≥ 4.5	25
Graft CD3+ cell dose, $x10^8$/kg Median, range	2.3 (0.8 to 4.1)
HCT-CI †	
0	0
1-2	10
≥3	12
Follow up, median (range) months	24 (3 to 87)

aDRI indicates adapted Disease Risk Index; AML, acute myeloid leukemia; ATG, antithymocyte globulin; CLL, chronic lymphocytic leukemia; DRI, Disease Risk Index; HCT-CI: hematopoietic cell transplantation-specific comorbidity index; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; MM, multiple myeloma; RIC, reduced-intensity conditioning.

† As pre-transplant pulmonary function tests were not systematically performed before 2006 in our institution, the HCT-CI was only assessable for patients who underwent PB-HSCT after January 2006 (22 patients in the MRD≥60y cohort).

Table S3. Subgroups analyses. Multivariate models for (A) patients for whom we were able to calculate the HCT-CI (N= 258) and for (B) patients aged of ≥50 years (N=199).

Pre-transplant variable	(A) HCT-CI cohort		(B) Older patients cohort	
	Overall mortality	Treatment failure	Overall mortality	Treatment failure
	HR (95%CI) P	HR (95%CI) P	HR (95%CI) P	HR (95%CI) P
Donor type/age				
MUD	1	1	1	1
MRD<60y §				
<6 mo	0.49 (0.22 - 1.06) 0.07	0.84 (0.48 - 1.50) 0.56	0.52 (0.25 - 1.08) 0.081	0.67 (0.36 - 1.27) 0.22
6 – 9 mo	0.95 (0.35 - 2.55) 0.92	0.48 (0.20 - 1.16) 0.10	1.22 (0.22 - 6.72) 0.82	0.46 (0.16 - 1.32) 0.15
9 – 18 mo	0.63 (0.22 - 1.80) 0.39	1.07 (0.35 - 3.31) 0.90	0.79 (0.31 - 2.00) 0.62	1.61 (0.58 - 4.48) 0.36
≥ 18 mo	0.97 (0.29 - 3.31) 0.96	1.02 (0.26 - 3.91) 0.98	0.96 (0.33 - 2.79) 0.94	1.45 (0.43 - 4.93) 0.55
MRD≥60y §				
<6 mo	0.16 (0.020 - 1.27) 0.083	0.50 (0.14 - 1.74) 0.28	0.55 (0.19 - 1.55) 0.26	1.05 (0.47 - 2.35) 0.91
6 – 9 mo	0.38 (0.044 - 3.23) 0.38	0.74 (0.16 - 3.41) 0.70	1.75 (0.24 - 12.7) 0.58	0.56 (0.12 - 2.69) 0.47
9 – 18 mo	3.95 (1.23 - 12.7) 0.021	4.79 (1.23 - 18.6) 0.024	1.51 (0.50 - 4.53) 0.46	3.07 (0.92 - 10.2) 0.069
≥18 mo	7.35 (1.25 - 43.3) 0.027	16.7 (2.46 - 113.5) 0.004	3.09 (0.93 - 10.2) 0.065	5.19 (1.12 - 24.0) 0.035
Recipient age, years				
< 20	0.36 (0.07 - 1.74) 0.20	N/C	N/A	N/A
20 – 29	1	N/C	N/A	N/A
30 – 39	0.71 (0.22 - 2.25) 0.56	N/C	N/A	N/A
40 – 49	0.86 (0.36 - 2.06) 0.74	N/C	N/A	N/A
50 – 59	0.88 (0.39 - 2.01) 0.76	N/C	N/A	N/A
≥ 60	1.61 (0.64 - 4.09) 0.31	N/C	N/A	N/A
HCT-CI				
0	1	1	N/C	N/C
1-2	0.59 (0.27 - 1.28) 0.18	0.78 (0.40 - 1.52) 0.46	N/C	N/C
≥3	0.68 (0.36 - 1.31) 0.25	0.88 (0.49 - 1.57) 0.67	N/C	N/C
DRI				
Low	0.61 (0.31 - 1.19) 0.15	0.71 (0.39 - 1.31) 0.28	0.78 (0.42 - 1.45) 0.43	0.79 (0.44 - 1.42) 0.43
Intermediate	1	1	1	1
High	0.74 (0.41 - 1.34) 0.32	1.18 (0.74 - 1.91) 0.48	0.92 (0.54 - 1.56) 0.76	1.18 (0.74 - 1.89) 0.49
Very high	3.83 (1.69 - 8.72) 0.001	3.03 (1.39 - 6.63) 0.005	1.49 (0.67 - 3.31) 0.33	1.87 (0.90 - 3.86) 0.091
ATG				
No	N/C	1	N/C	1
Yes	N/C	1.25 (0.76 to 2.04) 0.38	N/C	1.02 (0.62 - 1.68) 0.93
CD34+ cell dose				
≤ 4.5 x 10^6/kg	1	1	1	1
> 4.5 x 10^6/kg	0.58 (0.33 - 1.03) 0.062	0.75 (0.45 - 1.25) 0.27	0.35 (0.21-0.59) <0.0001	0.53 (0.33 - 0.85) 0.008
CD3+ cell dose				
< 2 x 10^8/kg	1	1	1	1
2 – 3 x 10^8/kg	0.70 (0.41 - 1.19) 0.18	0.73 (0.45 - 1.18) 0.19	0.74 (0.44 - 1.24) 0.25	0.87 (0.54 - 1.40) 0.57
> 3 x 10^8/kg	0.61 (0.35 - 1.07) 0.084	0.68 (0.42 - 1.11) 0.12	0.72 (0.41 - 1.25) 0.24	0.84 (0.51 - 1.38) 0.49
D/R CMV status				
Negative/Negative	1	N/C	1	N/C
Negative/Positive	0.88 (0.48 - 1.63) 0.69	N/C	1.55 (0.79 - 3.03) 0.2	N/C
Positive/Negative	0.59 (0.27 - 1.26) 0.17	N/C	1.05 (0.48 - 2.30) 0.90	N/C
Positive/Positive	0.65 (0.35 - 1.20) 0.17	N/C	1.63 (0.87 - 3.06) 0.13	N/C

ATG indicates antithymocyte globulin; CI, confidence interval; CMV, cy-megalovirus; D/R, donor/recipient; DRI, Disease Risk Index; HCT-CI, hema-poietic cell transplantation-specific comorbidity index; HR: hazard ratio; mo, months after transplant; MRD, matched related donor; MUD, matched unrelated donor; N/A, not applicable; N/C, not considered; OS, overall survival; PFS, progression free survival.

Table S4. Multivariate analysis of adapted DRI (aDRI) for OS, PFS, relapse and NRM.

aDRI	OS‡	PFS†	NRM¶	Relapse*
	HR (95%CI) *P*	HR (95%CI) *P*	HR (95%CI) *P*	HR (95%CI) *P*
Low	0.79 (0.50 to 1.24) 0.31	0.82 (0.54 to 1.24) 0.35	1.56 (0.91 to 2.68)0.11	0.38 (0.18 to 0.79) 0.010
Intermediate	1	1	1	1
High	1.38 (0.95 to 1.99) 0.090	1.58 (1.16 to 2.16) 0.004	1.58 (0.94 to 2.64) 0.085	1.63 (1.05 to 2.51) 0.028
Very High	1.36 (0.71 to 2.63) 0.36	2.05 (1.14 to 3.70) 0.017	1.21 (0.42 to 3.51) 0.72	2.54 (1.23 to 5.21) 0.011

aDRI indicates "Adapted Disease Risk Index"; CI, CI, confidence interval; HR, hazard ratio.

‡ adjusted for donor type/age group, recipient age, graft CD34+ and CD3+ cell doses and donor/recipient CMV sero-status match

† adjusted for donor type/age group, use of ATG and graft CD34+ and CD3+ cell doses

¶ adjusted for donor type/age group, recipient age, intensity of conditioning, graft CD34+ and CD3+ cell doses

* adjusted for donor type/age group, intensity of conditioning, use of ATG, graft CD3+ cell dose and donor/recipient ABO match

SUPPLEMENTAL FIGURES

Figure S1. Outcomes of patients with multiple myeloma (MM) and myeloproliferative neoplasms (MPN) as compared with disease type risk categories (first step of DRI determination). OS (A), PFS (B) and cumulative incidence of relapse (C).