Allogeneic hematopoietic stem cell transplantation after reduced intensity conditioning regimen for elderly patients (60 years and older) with hematologic malignancies using unrelated donors: a retrospective study from the French society for stem cell transplantation (SFGM-TC)

The use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) from unrelated donors (URD) has drastically increased in the past years. To date, there are limited data on the feasibility and outcomes of allo-HSCT from URD in patients aged 60 years and older. We report here results of a retrospective multicenter study that involved 516 consecutive patients aged 60 years or more [142 (28%) aged 65 years or more] who received a first allo-HSCT for hematologic malignancies [335 (65%) with myeloid disorders and 181 (35%) with lymphoid malignancies] between 2008 and 2012 in France. Two groups of patients were defined: 1) patients with age at allo-HSCT less than 65 years old ("URD<65 group", n=374); and 2) patients aged 65 years old or more ("URD ≥ 65 group", n=142). Patients' characteristics were similar between the 2 age groups (Table 1). HSC source was URD (HLA matched at HLA-A, -B, -C, -DQ and –DRB1, 10 out of 10 alleles in 95% of cases); peripheral blood stem cells were used in 92% of cases. All patients received reduced intensity conditioning (RIC)[1] that was fludarabine based in 91% of cases.

Most patients received a conditioning regimen containing intravenous busulfan at a total dose of 3.2 mg/kg (n=335, 65%) and fludarabine dosed at 120 mg/m² total (91% of patients).[2-4] Thirty-three (6%) patients received a combination of melphalan at 140 mg/m² and fludarabine. Three hundred and ninety-four patients (76%) received anti-thymocyte globulin (ATG), and 101 (20%) patients received 2Gy total body irradiation (TBI).[5,6] Use of the reduced intensity conditioning (RIC) regimen was based on institution norms, physician's choice, patient's age, comorbidities, prior HSCT, and enrollment in specific clinical trials. The median CD34⁺ cell dose was 5.0x10⁶ cells/kg (range 2-22). Median donor age was 35 years; 71% males. Graft-*versus*-host disease (GvHD) prophylaxis consisted of cyclosporine A (CsA) plus mycophenolate mofetil (MMF) in 47% of cases and CsA plus methotrexate in 20% of cases.

Of the 516 patients in this study, 7 patients died before engraftment: 5 patients (2%) in the URD<65 group and 2 patients (2%) in the URD≥65 group. Data were missing for 63 patients. The other patients achieved neutrophil and platelet engraftment.

Chimerism was measured by standard short tandem repeat (STR) genotyping analysis, and the median all-cell donor chimerism among patients who engrafted was 63% who achieved more than 95% all-cell donor chimerism by three months after allo-HSCT. At time of neutrophil engraftment, there was no difference between the 2 groups in terms of reaching a full donor cell chimerism with 62% *versus* 66%, respectively (*P*=0.6728).

The cumulative incidence of grades II-IV acute graft-*versus*-host disease (aGvHD) was 32% at one year for the 2 groups. The cumulative incidence of chronic graft-*versus*-host disease (cGvHD) was 25% at one year and 29% at two years after transplantation, and was also the same for the two groups. In multivariate analysis, lymphoid disease and HLA mismatch unrelated donor (MMUD) were associated with a higher incidence of aGvHD: hazard ratio (HR) (95%CI) myeloid *versus* lymphoid: 1.44 (1.01; 2.07), *P*=0.0440 and MUD *versus* MMUD: 2.59 (1.25; 5.37), *P*=0.0105). In contrast, only the use of ATG in the conditioning regimen had a trend to being correlated with a low incidence of aGvHD: HR Yes *versus* No: 1.47 (0.99; 2.18; *P*=0.0587). Age by itself at transplant did not have any impact on GvHD (*P*=0.6174 for cGvHD and *P*=0.4955 for aGvHD).

Median follow up was 36 months (range 0.3-73.5) for the URD<65 group and 32 months (range 0.03-72) for the URD≥65 group. The 2-year probabilities of overall survival (OS), progression-free survival (PFS), non-relapse

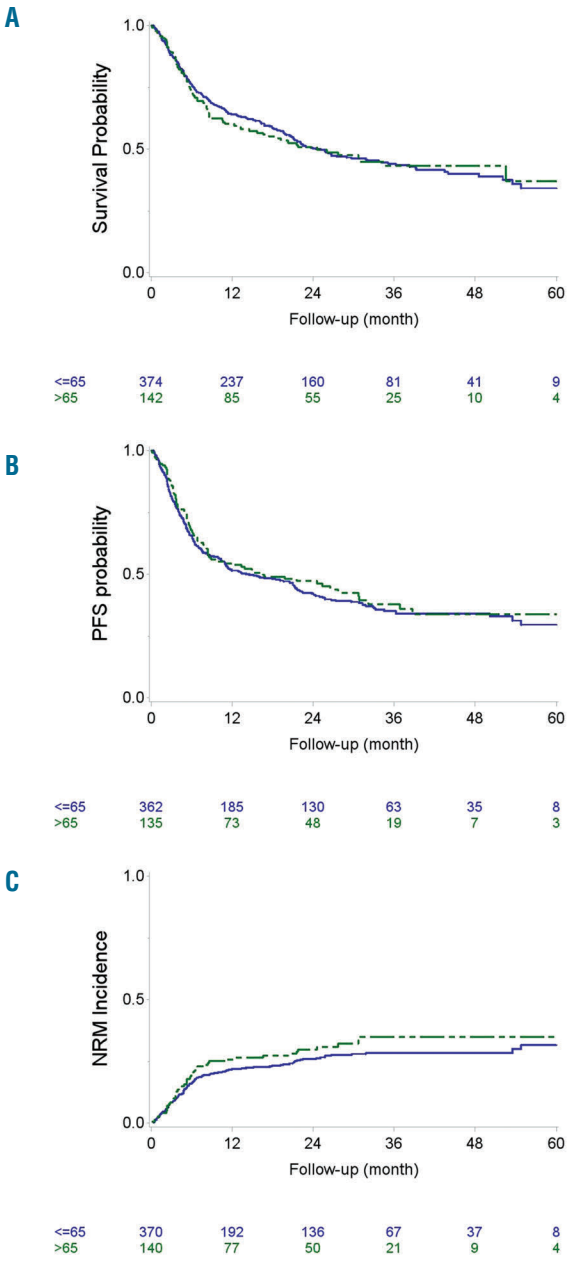

Figure 1. (A) **Overall survival according to patients' age.** (B) Progression-free survival according to patients' age. (C) Non-relapse mortality according to patients' age. Values under the graph represent patients at risk.

Table 1. Characteristics of the 516 patients according to recipient's age. Data are presented as (median) or number.

Characteristics	All patients (n=516)	Age≤65 (n=374)	Age>65 (n=142)	P
Age (years)	63.10 (60.02-73.74)	62.11 (60.02-64.99)	66.44 (65.01-73.74)	<0.001
Sex				
Male	311 (60.27)	231 (61.76)	80 (56.34)	0.2606
Female	205 (39.73)	143 (38.24)	62 (43.66)	
Diagnosis				0.0448
Acute myeloid leukemia	157 (30.43)	104 (27.81)	53 (37.32)	
Acute lymphoblastic leukemia	13 (2.52)	10 (2.67)	3 (2.11)	
Myelodysplastic syndromes	91 (17.64)	57 (15.24)	34 (23.94)	
Myeloproliferative neoplasms	14 (2.71)	11 (2.94)	3 (2.11)	
Chronic myeloid leukemia	5 (0.97)	2 (0.53)	3 (2.11)	
Chronic lymphocytic leukemia	43 (8.33)	37 (9.89)	6 (4.23)	
Non-Hodgkin lymphoma	68 (13.18)	52 (13.90)	16 (11.27)	
Hodgkin lymphoma	1 (0.19)	1 (0.27)		
Multiple myeloma	56 (10.85)	43 (11.50)	13 (9.15)	
Other	32 (6.20)	28 (7.49)	4 (2.82)	
Time between diagnosis and graft (months)	15.69 (1.48-484.2)	13.72 (1.48-223.6)	17.46 (3.25-484.2)	0.570
≤12	218 (42.25)	157 (41.98)	61 (42.96)	0.8406
>12	298 (57.75)	217 (58.02)	81 (57.04)	
Myeloid or lymphoid disease				
Myeloid	335 (64.92)	231 (61.76)	104 (73.24)	0.0147
Lymphoid	181 (35.08)	143 (38.24)	38 (26.76)	
Number of infused total nucleated cells (x10^6/kg)	50.5 (7.00-1281)	50.5 (7.00-1281)	82.0 (8.00-860.0)	0.962
Number of CD34 cells (x10^6/kg)	5.00 (2.00-22.0)	5.00 (4.00-22.0)	5.00 (4.00-13.0)	0.352
Disease status				
Early (≥ partial response)	334 (65.62)	238 (64.32)	96 (69.06)	0.3158
Advanced (< partial response)	175 (34.38)	132 (35.68)	43 (30.94)	
HLA compatibility				
Matched unrelated	497 (96.32)	358 (95.72)	139 (97.89)	0.2434
Mismatched unrelated	19 (3.68)	16 (2.11)	3 (4.28)	
Graft source				
Peripheral blood	477 (92.44)	342 (91.44)	135 (95.07)	0.1640
Bone marrow	39 (7.56)	32 (8.56)	7 (4.93)	
Chemo before conditionning				
Fludarabine + total body irradiation	100 (19.38)	70 (18.72)	30 (21.13)	0.2346
Busulphan + fludarabine + melphalan	335 (64.92)	238 (63.64)	97 (68.31)	
Fludarabine + melphalan	33 (6.40)	28 (7.49)	5 (3.52)	
Other	48 (9.30)	38 (10.16)	10 (7.04)	
Conditioning regimen				
Non-myeloablative	76 (14.73)	52 (13.90)	24 (16.90)	0.3908
Reduced intensity conditioning	440 (85.27)	322 (86.10)	118 (83.10)	
Anti-thymoglobuline (ATG)				
Yes	394 (76.36)	286 (76.47)	108 (76.06)	0.9212
No	122 (23.64)	88 (23.53)	34 (23.94)	
Total body irradiation				
Yes	101 (19.57)	71 (18.98)	30 (21.13)	0.5838
No	415 (80.43)	303 (81.02)	112 (78.87)	
Graft-*versus*-host disease prophylaxis				
Cyclosporine A (CsA)	133 (25.98)	97 (26.08)	36 (25.71)	0.0729
Mycophenolate mofetil	28 (5.47)	14 (3.76)	14 (10.00)	
Cyclosporine A/mycophenolate mofetil	244 (47.66)	178 (47.85)	66 (47.14)	
Cyclosporine A/methotrexate	102 (19.92)	79 (21.24)	23 (16.43)	
Others	5 (0.98)	4 (1.08)	1 (0.71)	
EBMT score				
>2	384 (74.71)	277 (74.46)	107 (75.35)	0.8356
<=2	130 (25.29)	95 (25.54)	35 (24.65)	
Age of donor	35.21 (19.30-60.36)	35.21 (19.30-60.36)	35.13 (19.83-54.73)	0.7837
<=30	161 (35.23)	120 (35.61)	41 (34.17)	0.7765
>30	296 (64.77)	217 (64.39)	79 (65.83)	
Donor gender				
Male	364 (70.54)	255 (68.18)	109 (76.76)	0.1272
Female	150 (29.07)	117 (31.28)	33 (23.24)	
Sex mismatch (patient/donor)				
Same sex	302 (58.53)	217 (58.02)	85 (59.86)	0.6501
Different sex	212 (41.09)	155 (41.44)	57 (40.14)	
Cytomegalovirus status (patient/donor)				
Negative/negative	159 (30.81)	113 (30.21)	46 (32.39)	0.6319
Others	357 (69.19)	261 (69.79)	96 (67.61)	

Table 2. Two-year estimations of outcomes for acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) patients.

	AML			MDS		
	Age≤65 (n=104)	Age>65 (n=53)	P	Age≤65 (n=57)	Age>65 (n=34)	P
OS*	0.54 (0.43-0.63)	0.56 (0.41-0.68)	0.763	0.46 (0.33-0.59)	0.49 (0.31-0.64)	0.901
PFS*	0.47 (0.37-0.57)	0.54 (0.39-0.67)	0.682	0.34 (0.22-0.46)	0.39 (0.22-0.55)	0.446
NRM**	0.22 (0.15-0.32)	0.26 (0.16-0.42)	0.513	0.25 (0.16-0.39)	0.36 (0.23-0.57)	0.317
Relapse**	0.24 (0.16-0.35)	0.16 (0.08-0.32)	0.571	0.35 (0.21-0.56)	0.23 (0.11-0.50)	0.293
aGvHD**	0.26 (0.18-0.36)	0.31 (0.21-0.47)	0.498	0.29 (0.19-0.44)	0.44 (0.30-0.65)	0.203
cGvHD**	0.33 (0.25-0.44)	0.35 (0.24-0.51)	0.787	0.34 (0.24-0.49)	0.19 (0.09-0.40)	0.171

*OS: overall survival; PFS: progression-free survival; NRM: non-relapse mortality; aGvHD: acute graft-*versus*-host disease; cGvHD: chronic graft-*versus*-host disease; *Kaplan Meier estimations and log rank test. **Prentice estimations and Fine and Gray test. Data are estimations (95% Confidence Interval).*

mortality (NRM), and relapse incidence (RI) for the whole population was 50%, 43%, 27% and 21%, respectively, with no significant difference observed between the two age groups (Figure 1A-C). In multivariate analysis advanced disease was associated with a higher risk of death and progression: HR (95%CI) 1.56 (1.19, 2.04), *P*=0.0013 and HR (95%CI) 1.65 (1.27, 2.14), *P*=0.0002, respectively. Age of donor 30 years or under was associated with a higher risk of relapse: HR (95%CI) 2.14 (1.33, 3.43). Moreover, patients with an EBMT score more than 2 had a higher rate of NRM [HR (95%CI) 2.31 (1.43-3.72), *P*=0.0006], as well as patients who did not receive ATG [HR (95%CI] 1.59 (1.10, 2.31) *P*=0.0136]. Age by itself had no influence on outcomes in multivariate analysis. Results concerning AML and MDS patients only are shown in Table 2.

These data suggest equivalence of outcome between the URD≤65 group and the URD>65 group after RIC URD allo-HSCT in this large cohort of elderly patients. Therefore, age by itself appears not to be a limitation to proceed to allo-HSCT.

In this large national multi-center retrospective study, we report the French experience with 516 consecutive patients over the age of 60 years who received an allo-HSCT from URD between 2008 and 2012. Our main finding is an equivalence of outcomes between patients aged less than 65 years and those aged 65 years or older who received an RIC unrelated allo-HSCT. Therefore, age by itself did not play a role in this large cohort of elderly patients.

For older patients, in particular for those over 60 years of age, the availability of a suitable sibling donor is further limited by the concordant increased age of their siblings. Even though older patients are typically ineligible for myeloablative allo-HSCT, they can frequently be considered for a non-myeloablative transplant approach. In this context, our findings of comparable outcomes in the 2 groups of patients (URD<65 group and URD≥65 group) after an RIC regimen using an unrelated donor are important because they suggest that, in the absence of suitable related donors, well-matched URD may offer a very reasonable alternative. Based on our results, URD allo-HSCT appears to be an effective and tolerable option for carefully selected adults over the age of 60 years, with an encouraging low cumulative incidence of NRM of 29% at two years, as well as a 2-year PFS of 43% and 2-year OS of 50%.

A large study performed by the Center for International Blood and Marrow Transplant Research (CIBMTR) studied patients older than 65 years undergoing RIC allo-HSCT, including 63 AML and 55 MDS.[7] In that study, which included patients up to the age of 79 years receiving allo-HSCT from both identical siblings and URD, authors concluded that age by itself did not adversely affect TRM, relapse, PFS, or OS. This was also described in a prior series of patients over 60 years of age treated with RIC regimens at the Dana-Farber Cancer Institute.[4] Patients over 65 years of age (range 65-71 years) at transplantation did not have a worse outcome than those aged 60 to 65 years in terms of TRM, relapse, OS, or PFS; a finding confirmed in a similar retrospective study of 600 patients from our group in France.[8] Our study adds to the literature by reporting survival outcomes in the largest series of patients over 60 years of age who underwent transplantation from URD with current conditioning regimens.

It is most notable that the incidence of both NRM and aGvHD were low in our cohort of patients. The observed rate of grades II to IV is comparable with our previously described RIC cohorts.[4,9] Our observed low incidence of NRM and aGvHD in this elderly group likely reflects appropriate patient selection.

Given the retrospective nature of our analysis, and the heterogeneous patient population selected for transplantation, there is no control arm of comparably aged patients who were either deemed unfit for allo-HSCT or who were treated with alternative therapies. Thus, we are unable to assess whether allo-HSCT improved the prognosis of such patients, although, in this study, URD was used only when an MRD was not available. Moreover, we were not able to retrieve specific co-morbidity scores in this large cohort of patients. Given these considerations, one may question the desirability of older MRD when a healthier, younger matched URD is available. In our analysis, we found that the median age of URD (≤30years) had indeed a significant impact on the outcome with high risk of relapse, but we are unable to provide an explanation for this (*P*<0.0017). Conversely, our analysis is strengthened by its large population and the fact that both the URD cohorts (URD<65 group and URD≥65 group) had the same extended follow up and were well balanced at the time of transplant, disease characteristics, disease risk, prior autologous transplants, conditioning regimen, and GvHD prophylaxis regimens.

In conclusion, our data suggest equivalence of outcome between the URD<65 group and the URD≥65 group after RIC URD allo-HSCT in a large cohort of elderly patients (>60 years) with hematologic malignancies. When treating this particular population of elderly patients aged 65 years and over with a reasonable performance status and comorbidity profile, age by itself should not, therefore, appear as a limitation to proceed to allo-HSCT. Finally, future studies will also have to focus on other more qualitative outcomes such as cost-effectiveness and quality of

life, because various complications may be much more expensive and difficult to treat in older patients than their younger counterparts.

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The online version of this letter has a Supplementary Appendix.

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doi:10.3324/haematol.2015.139345

Key words: allogeneic stem cell transplantation, elderly patients, unrelated donors.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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