Allogeneic − Adult

Allogeneic Hematopoietic Cell Transplantation in Patients Aged 50 Years or Older with Severe Aplastic Anemia

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A B S T R A C T

We report on 499 patients with severe aplastic anemia aged $\geq$ 50 years who underwent hematopoietic cell transplantation (HCT) from HLA-matched sibling (n = 275, 55%) or HLA-matched (8/8) unrelated donors (n = 187, 37%) between 2005 and 2016. The median age at HCT was 57.8 years; 16% of patients were 65 to 77 years old. Multivariable analysis confirmed higher mortality risks for patients with performance score less than 90% (hazard ratio [HR], 1.41; 95% confidence interval [CI], 1.03 to 1.92; $P = .03$) and after unrelated donor transplantation (HR, 1.47; 95% CI, 1 to 2.16; $P = .05$). The 3-year probabilities of survival for patients with performance scores of 90 to 100 and less than 90 after HLA-matched sibling transplant were 66% (range, 57% to 75%) and 57% (range, 47% to 76%), respectively. The corresponding probabilities after HLA-matched unrelated donor transplantation were 57% (range, 48% to 67%) and 48% (range, 36% to 59%). Age at transplantation was not associated with survival, but grades II to IV acute graft-versus-host disease (GVHD) risks were higher for patients aged 65 years or older (subdistribution HR [sHR], 1.7; 95% confidence interval, 1.07 to 2.72; $P = .026$). Chronic GVHD was lower with the GVHD prophylaxis regimens calcineurin inhibitor (CNI) + methotrexate (sHR, .52; 95% CI, .33 to .81; $P = .004$) and CNI alone or with other agents (sHR, .27; 95% CI, .14 to .53; $P < .001$) compared with CNI + mycophenolate. Although donor availability is modifiable only to a limited extent, choice of GVHD prophylaxis and selection of patients with good performance scores are key for improved outcomes.

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INTRODUCTION

Treatment algorithms for severe aplastic anemia (SAA) are not well characterized for older patients. For older patients treatment decisions are based not only on disease factors but also on their health and functional ability to reduce the risk of treatment-related toxicity that may contribute to morbidity and mortality [1]. For these reasons hematopoietic cell transplantation (HCT) in older patients with SAA is usually only considered as second-line treatment [2].

Existing data on outcomes after HCT or immunosuppressive therapy (IST) have examined different age groups, >40 years for HCT [3,4] and >60 years for IST [5-7]. First-line IST using horse antithymocyte globulin (ATG) and cyclosporine in patients aged > 60 years is associated with a similar response as that in younger patients, but survival is worse in older patients [5,7,8]. Although HLA-matched related and unrelated donor transplantations are offered to patients who are fit and as first-line treatment for matched related or those who fail first-line IST for matched unrelated donor HCT, increasing age at transplantation (>40 years) remains a concern [4-6]. However, a recent report on 115 adults failed to show a difference in survival after HLA-matched sibling transplantation [9]. A second course of IST is effective in only a third of cases and increases the risk of later progression to myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) [10,11]. The recent use of eltrombopag for refractory SAA is effective in 40% of patients, although 19% of patients reported early onset of abnormal cytogenetic clones (most commonly monosomy 7) [12].

A retrospective natural history study of aplastic anemia covering the whole of Sweden has highlighted the significantly worse survival for patients aged $\geq$ 60 years compared with younger patients where less than 40% were alive after 5 years and with a relative 5-year survival (excess mortality) of 45% [13]. Hence, there is an unmet need to improve the management of this older group of patients with aplastic anemia. However, no data specifically address HCT outcomes in a relatively large cohort of SAA patients older than 50 years. Herein we report for the first time a cohort of 499 SAA patients older than 50 years at transplantation and reported to the European Society for Blood and Marrow Transplant (EBMT) or the Center for International Blood and Marrow Transplant Research (CIBMTR).

METHODS
Patients

Data on patients were obtained from 2 international transplant registries, the CIBTMR and the EBMT. Both registries collect data on consecutive transplantations performed at participating sites, and patients are followed longitudinally until death or loss to follow-up. Transplantations occurred between 2005 and 2016 in Europe or North America. Ethical approval for studying transplantations reported to the EBMT was granted by the EBMT SAA Working Party. The Institutional Review Board of the National Marrow Donor Program approved studying transplantations reported to the CIBMTR and this study.

Inclusion Criteria

Eligible patients were aged 50 years or older with SAA and transplanted from an HLA-matched sibling or adult matched unrelated donor (8/8 reported or 8/8 high resolution). Patients transplanted from a haploidentical donor, umbilical cord blood, or who reported a prior HCT were excluded.

Endpoints

Primary endpoint was overall survival. Death from any cause was considered an event, and surviving patients were censored at 36 months, based on the median follow-up for this study: 42 months (range, 37 to 49). Neutrophil engraftment was defined as achieving an absolute neutrophil count $\geq$ .5 × 10^9/L for 2 consecutive days, before day 28. Platelet recovery was defined as achieving an unsupported platelet count of $\geq$20 × 10^9/L for 7 days, before day 100. Engraftment failure included primary and secondary graft failure captured through day 100 and defined as failing to achieve absolute neutrophil count $\geq$ .5 × 10^9/L, donor chimerism < 5%, subsequent loss of absolute neutrophil count to <.5 × 10^9/L, or second infusion. Grades II to IV acute and chronic graft-versus-host disease (GVHD) was defined according to standard criteria [14,15].

Statistical Analysis

The probability of overall survival was calculated using the Kaplan-Meier product limit estimation method, and differences in subgroups were assessed by the log-rank test. All estimates of overall survival are provided at 36 months post-transplant and are reported with corresponding 95% confidence intervals (CIs). Median follow-up was determined using the reverse Kaplan-Meier method. Cox proportional hazards regression was used to assess the impact of potential risk factors on mortality in multivariable analyses, providing hazard ratios (HRs) with their 95% CIs. The incidences of hematopoietic recovery, acute and chronic GVHD, and primary and secondary graft failure were calculated in a competing risk framework. Competing events for each outcome were mortality, no engraftment, relapse, and second transplant. Subgroup differences were assessed by Gray's test. Multivariable Fine and Gray regression was used to study risk factors associated with acute and chronic GVHD, providing subdistribution HRs (sHR) with 95% CIs. All P values were w-sided, and $P \leq$ .05 was considered significant. All analyses were performed in SPSS 23 (Armonk, NY, USA) and in R 3.3.2 (R Development Core Team, Vienna, Austria) using packages "survival," "prodlim," and "cmprsk."

RESULTS
Patient and Transplant Characteristics

Patient and transplant characteristics are summarized in Table 1. Comparison of patient characteristics and outcomes between EBMT and CIBMTR registries are summarized in the Supplementary Material. The median age at transplantation was 57.8 years (range, 50 to 77.7). Of 499 patients, most (n = 420; 84%) were aged 50 to 64 years and only 16% (n = 79) were 65 years or older. Fifteen patients were 70 years or older, accounting for only 3% of the patient population.

Karnofsky performance scores of 90 or 100 were observed in 49% of patients. Sixty-seven percent of patients were cytomegalovirus seropositive, and 38.5% of transplantations (median, 10; range, <1 to 357) occurred at least a year after diagnosis. Of the patients with available IST information, 89.6% received at least 1 course of prior immune suppressive treatment. Fifty-five percent of patients received their graft from an HLA-matched sibling and 38% from an HLA-matched unrelated donor. For the remaining 7% the degree of mismatching was unknown. Approximately equal numbers of patients received bone marrow (53%) and peripheral blood (47%) grafts.

Cyclophosphamide with ATG alone or with ATG and fludarabine were the predominant conditioning regimens for HLA-matched sibling HCT, whereas for unrelated donor HCT cyclophosphamide with total body irradiation 200 cGy and ATG or with the inclusion of fludarabine were mostly used. Most patients received calcineurin inhibitor (CNI)-containing GVHD prophylaxis. Among the 117 patients who received CNI + mycophenolate mofetil (MMF), 53 (45%) received an ATG-containing and 5 (4%) received an alemtuzumab-containing conditioning regimen. Similarly, 101 of 246 patients (41%) who received CNI + methotrexate (MTX) received ATG-containing and 7 (3%), alemtuzumab-containing conditioning regimens. Forty-seven of 110 patients (43%) who received CNI alone or other agents for GVHD prophylaxis received an alemtuzumab-containing and 33 of 110 (30%) received an ATG-conditioning regimen.

Because unrelated donor transplants were more recent, the median follow-up was 38 months (range, 36 to 45) and that after HLA-matched sibling transplants, 49 months (range, 38 to 58). The median follow-up of the combined population was 42 months (range, 37 to 49), and outcomes were censored at 36 months to accommodate differential follow-up.

Table 1
Patient Characteristics

Characteristic	Subcategory	No. of Cases or Median	Percent or Range
Registry	CIBMTR	194	38.9
	EBMT	305	61.1
Age	≥65 yr	79	15.8
	50-64 yr	420	84.2
Patient sex	Female	245	49.1
	Male	254	50.9
Performance score	<90%	190	38.1
	90-100%	243	48.7
	Missing	66	13.2
Patient cytomegalovirus	Negative	126	25.3
	Positive	335	67.1
	Missing	38	7.6
Interval from diagnosis to treatment	≤12 yr	307	61.5
	>12 yr	192	38.5
Donor	Matched unrelated	187	37.5
	HLA-identical sibling	275	55.1
	Missing	37	7.4
Graft source	Bone marrow	266	53.3
	Peripheral blood	233	46.7
Regimen	Cy + ATG	91	18.2
	Cy + Flud ± ATG	92	18.4
	TBI 200 + Cy + Flud + ATG	57	11.4
	TBI 200 + Cy ± ATG	28	5.6
	Alkylating agent + Flud ± ATG	65	13
	Alemtuzumab	60	12
	Flud + Cy + alemtuzumab	40	
	Alemtuzumab + other	20	
	Other non-TBI regimen	73	14.6
	Other TBI regimens	18	3.6
	Missing	15	3
GVHD prophylaxis	CNI + MMF	117	23.4
	CNI + MTX	246	49.3
	CNI ± other drug	67	13.4
	Other	43	8.6
	Missing	26	5.2
HSCT year	2005-2009	191	38.3
	2010-2014	308	61.7
Age, yr	Median (range)	499	57.8 (50-77.7)
Interval from diagnosis to treatment, yr	Median (range)	499	.8 (<1-29.7)
Follow-up	Median (95% CI)		42.4 (37.2-48.9)

Cy indicates cyclophosphamide; Flud, fludarabine; TBI, total body irradiation.

Hematologic Recovery

The incidence of primary graft failure at 100 days was 10% (range, 7-12%). The incidence of secondary graft failure at 36 months after transplantation among patients with initial engraftment was 7% (range, 4% to 10%). Day 28 cumulative incidence of neutrophil recovery was 82% (range, 79% to 86%). Multivariable analysis for risk factors associated with neutrophil recovery is shown in Table 2. Neutrophil recovery was higher in patients receiving peripheral blood grafts compared with bone marrow (sHR, 1.74; 95% CI, 1.38 to 2.2; $P < .001$) and lower in patients receiving CNI + MTX compared with CNI + MMF as GVHD prophylaxis (sHR, .59; 95% CI, .44 to .8; $P < .001$).

Overall Survival

The 3-year probability of overall survival for the entire cohort was 56% (range, 52% to 61%) and was 59% (range, 53% to 66%) and 52% (range, 45% to 60%) for matched related and matched unrelated donor HCT, respectively. The 3-year probabilities of survival for patients with performance scores of 90 to 100 and <90 after HLA-matched sibling transplant were 66% (range, 57% to 75%) and 57% (range, 47% to 76%), respectively (Figure 1). The corresponding probabilities after unrelated donor transplantation were 57% (range, 48% to 67%) and 48% (range, 36% to 59%) (Figure 1). None of the other variables tested, including age at HCT, cytomegalovirus serostatus, graft

type, interval between diagnosis and HCT, and transplant period, attained the level of significance set for this study.

Multivariable analysis confirmed higher mortality risks for patients with a performance score of less than 90% and recipients of unrelated donor HCT (Table 2). The effects of performance score and donor type on overall survival were independent of each other.

There was no significant difference in mortality risk for older patients aged 65 to 78 years compared with those aged 50 to 64 years (HR, 1.20; 95% CI, .81 to 1.81; $P = .343$). There were 215 deaths; infection was the predominant cause of death, accounting for 40% of deaths followed by GVHD (13%), multiorgan failure (10%), and graft failure (9%). Other causes included malignancy, including Epstein-Barr virus associated post-transplant lymphoproliferative disease (5%), interstitial pneumonitis (1%), and other toxicities (7%). The cause of death was not reported for 15% of patients.

Graft-versus-Host Disease

The day 100 incidence of acute GVHD in patients aged 50 to 64 years was 20% (range, 16% to 24%) and those aged 65 years and older, 35% (range, 24% to 46%; $P = .006$) (Figure 2A; see Figure 2B for chronic GVHD). The corresponding incidence for patients who received CNI + MMF was 33% (range, 24% to 42%), CNI + MTX 24% (18% to 29%), and CNI alone or other GVHD prophylaxis regimens 13% (range, 7% to 20%), respectively

Table 2
Risk Factors for Overall Survival and Neutrophil Recovery

Risk Factor	Subcategory	No. of Cases	No. of Events	HR (95% CI)	P
	Overall survival				
	Total	424	164		
Registry	EBMT	246	88		
	CIBMTR	178	76	.98 (.71-1.36)	.918
Age	50-64 yr	354	132		
	≥65 yr	70	32	1.21 (.81-1.81)	.343
Patient sex	Male	216	88		
	Female	208	76	.82 (.6-1.12)	.205
Performance score	<90%	189	83		
	90-100%	235	81	.71 (.52-.97)	.03
GVHD prophylaxis	CNI + MMF	99	39		
	CNI + MTX	223	91	1.22 (.82-1.81)	.319
	Other	102	34	.86 (.54-1.38)	.537
Donor	Identical sibling	221	78		
	Unrelated donor	203	86	1.47 (1-2.16)	.05
Regimen	Non-TBI regimen	321	122		
	TBI regimen	103	42	.76 (.49-1.19)	.226
Graft source	Bone marrow	229	90		
	Peripheral blood	195	74	.96 (.7-1.32)	.813
Interval from diagnosis to treatment, yr		424		.99 (.94-1.05)	.818
				sHR (95% CI)	
	Neutrophil recovery				
	Total	406	368		
Registry	EBMT	232	210		
	CIBMTR	174	158	1.32 (1.06-1.65)	.014
Age	50-64 yr	337	307		
	≥65 yr	69	61	.95 (.7-1.3)	.76
Performance score	<90%	181	158		
	90-100%	225	210	1.24 (.99-1.54)	.062
Patient cytomegalovirus	Negative	114	105		
	Positive	292	263	1.13 (.91-1.41)	.27
GVHD prophylaxis	CNI + MMF	98	92		
	CNI + MTX	210	188	.59 (.44-.8)	<.001
	Other	98	88	.78 (.55-1.1)	.15
HSCT period	2005-2009	133	119		
	2010-2014	273	249	1.14 (.89-1.45)	.29
Donor	Identical sibling	210	189		
	Unrelated donor	196	179	.99 (.79-1.24)	.92
Graft source	Bone marrow	223	199		
	Peripheral blood	183	169	1.74 (1.38-2.2)	<.001

(Figure 2C). The results of multivariable analysis for risk factors associated with acute and chronic GVHD are shown in Table 3. Risk for grades II to IV acute GVHD was higher for patients aged 65 years and older and lower for those who received CNI alone or other agents compared with CNI + MMF (sHR, .48; 95% CI, .26 to .88; *P* = .018).

The 3-year incidences of chronic GVHD were 49% (range, 39% to 59%) with CNI + MMF, 31% (range, 24% to 38%) with CNI + MTX, and 18% (range, 9% to 26%) with CNI alone or other GVHD prophylaxis (*P* < .001) (Figure 2D). The only risk factor associated with chronic GVHD was GVHD prophylaxis regimen. Risks were lower with CNI + MTX (sHR, .52; 95% CI, .33 to .81; *P* = .004) and CNI alone or with other agents (HR, .27; 95% CI, .14 to .53; *P* < .001) compared with CNI + MMF.

DISCUSSION

Reported here is the first global study evaluating outcomes after matched related and matched unrelated donor HCT for SAA patients aged ≥ 50 years including 79 patients who were aged between 65 and 77 years. Patients undergoing second transplant were excluded from this study, making the data more specific and providing more accurate interpretation of graft failure, especially late graft failure. The current analyses support allogeneic transplantation as an acceptable treatment option for older adults who fail IST with careful attention to patient selection. The upper age limit for upfront matched

related HCT has been steadily rising over time as outcomes continue to improve. A cutoff at 35 to 50 years has been recommended, depending on patient comorbidities [2], although recently for patients aged 41 to 60 years it has been suggested that upfront transplantation might be carefully considered in selected patients who are medically fit [6]. Otherwise, first-line treatment for older patients is IST. In older patients who lack an HLA-matched related donor, HLA-matched unrelated donor HCT is only offered after failure to respond to IST.

We have shown that the 3-year survival exceeds 50% after related and unrelated donor HCT. Although unrelated donor HCT was independently associated with worse survival, the availability of a matched sibling is not a modifiable factor. Optimizing patient selection by considering referral after failure of 1 course of IST and initiation of donor search at diagnosis for those who are "fit" with good performance scores may mitigate mortality risks. We were not able to assess HCT-specific comorbidity index scores because of a lack of available data. We also examined for any interaction between performance status and age on clinical outcomes to demonstrate their separate effects (see Supplementary Material). Both acute and chronic GVHD were exceptionally low with alemtuzumab-containing conditioning regimens. Although patient numbers are small (60 patients received alemtuzumab-containing regimens), considering transplant strategies that include alemtuzumab may help lower the burden of morbidity and perhaps late mortality,
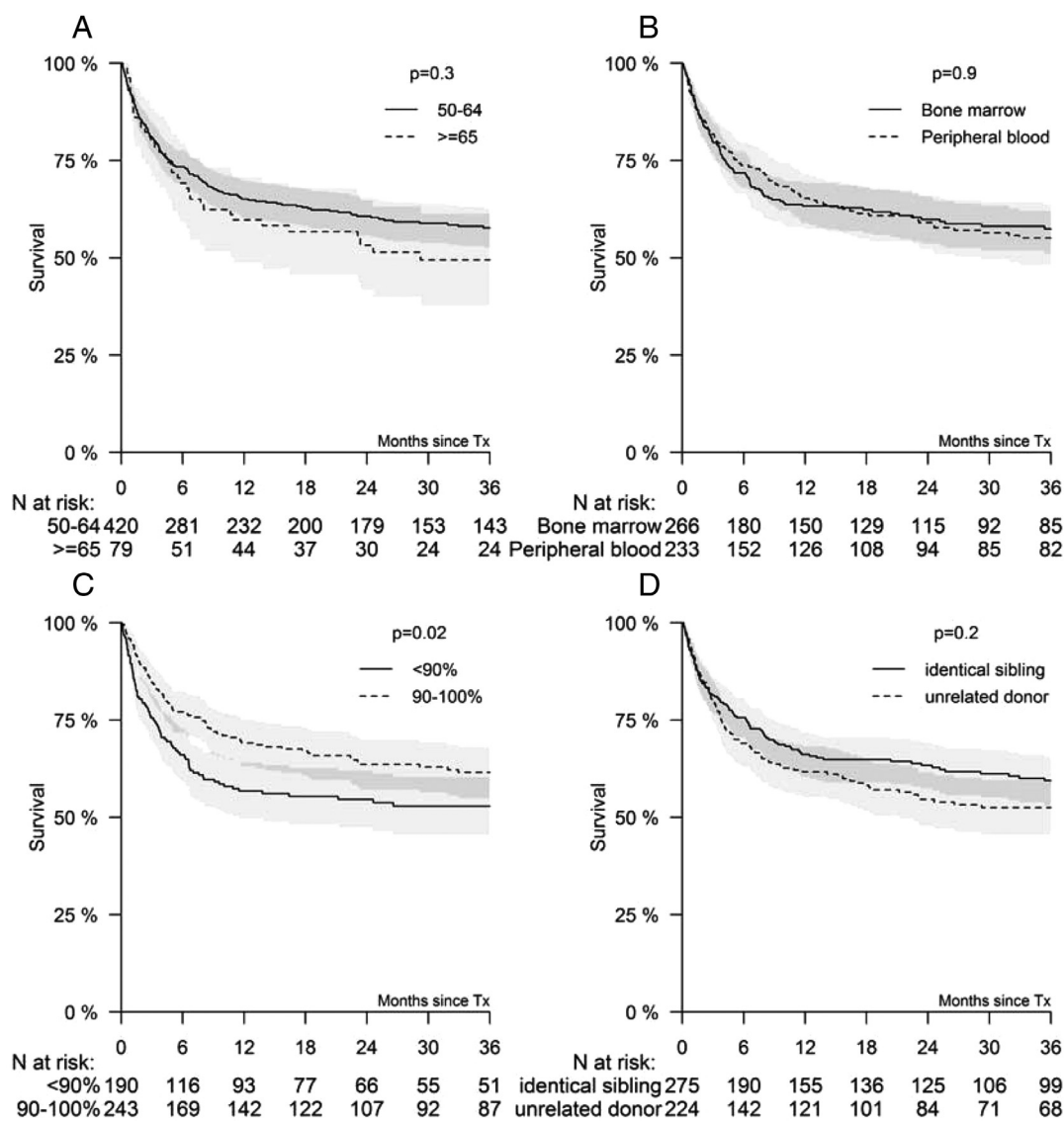
Figure 1. Factors affecting overall survival. (A) Overall survival by age < 65 versus ≥65 years. (B) Overall survival by by stem cell source. (C) Overall survival by performance status. (D) Overall survival by by donor type. The shaded regions indicate the corresponding 95% CIs. Reported *P* values are based on the log-rank test.

although mortality within the first 3 years after HCT was not associated with use of alemtuzumab. The other potential benefits of alemtuzumab instead of ATG are that addition of MTX to a CNI is not required, thus eliminating the risk of mucositis, reducing the risk of hepatotoxicity, and avoiding total body irradiation containing regimens even for unrelated donor HCT. Additionally, peripheral blood stem cells can be used with alemtuzumab because of very low GVHD with the added benefit of a higher incidence of engraftment [16,17].

Other studies that have examined the effect of donor type (younger unrelated donor or older sibling) have limited unrelated donor transplant recipients to those who received grafts from a young unrelated donor [18]. With the additional limitation of the unrelated donor transplant recipients to HLA-matched transplants, the study population was not adequately powered to detect differences in survival based on donor age.

The question of 1 versus multiple prior courses of IST was not addressed in the current analyses, because these data, along with number of prior transfusions, are not routinely captured in this registry-based retrospective study. Survival after IST is age dependent, with worse survival among older patients

compared with younger patients. A retrospective EBMT study of 242 patients aged > 50 years reported a 5-year survival of 57% for patients aged 50 to 59 years and 50% for ≥60 years [7]. A subsequent prospective randomized EBMT study of first-line ATG and cyclosporine with or without granulocyte colony-stimulating factor showed that for patients aged >60 years the 3- and 6-year overall survival was 65% and 56%, respectively [19]. In a national study from Sweden, 5-year survival for patients aged ≥ 60 years treated with IST from 2000 to 2011 was 52% [13]. Thus, survival after HLA-matched related HCT is comparable with that after IST therapy in this older age group. Other factors to consider with IST in older patients are, for example, that unlike in a younger population, use of ATG in older patients is associated with arrhythmia, cardiac failure, and sudden cardiac ischemic events, all of which adds to the burden of morbidity and mortality [3]. The next question is how survival after HLA-matched HCT compares with a second course of IST with ATG and cyclosporine or other ISTs such as alemtuzumab. Hematologic response occurs in only 30% to 40% of patients of all age groups after a second course of IST given for refractory SAA [10,20]. We are not aware of any published
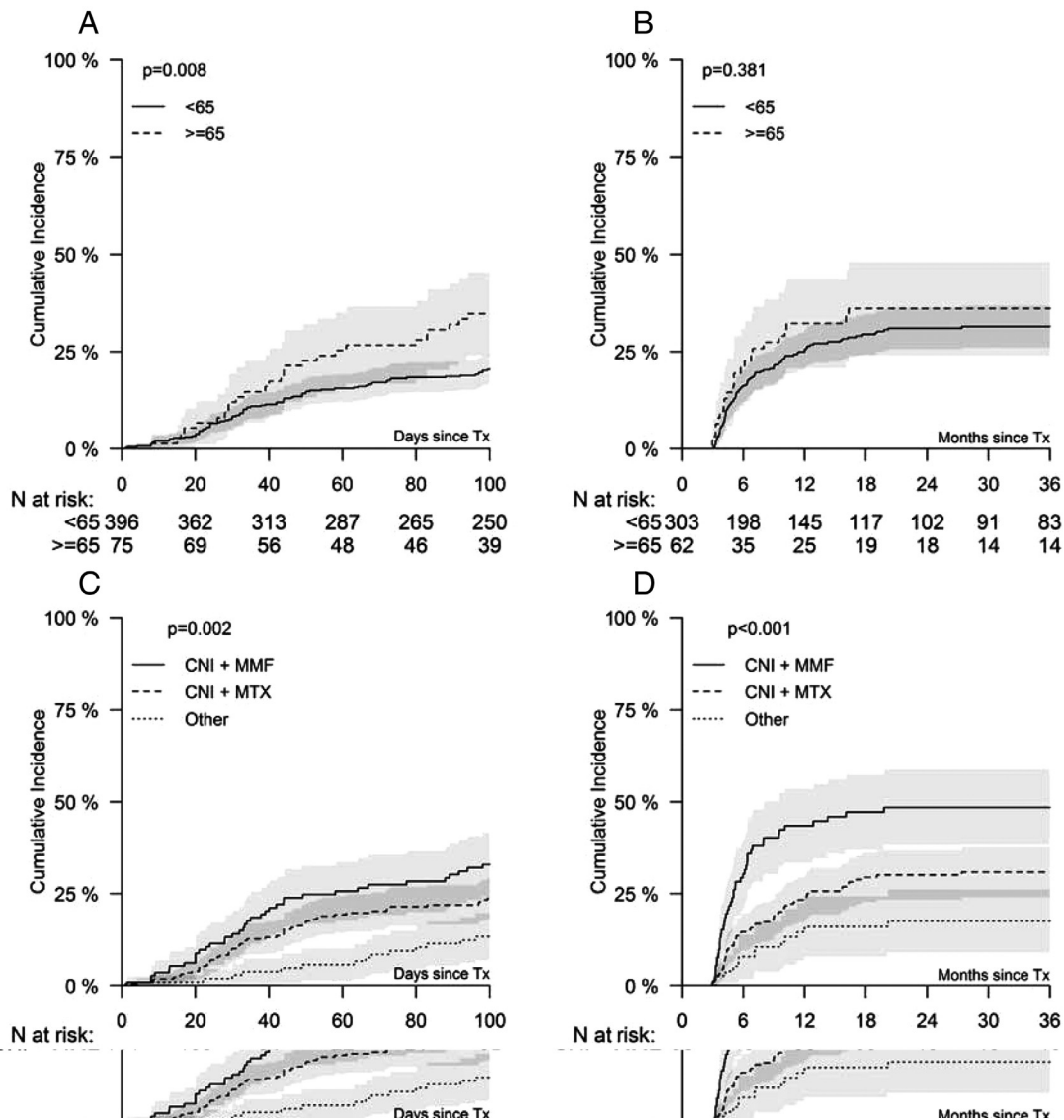
Figure 2. Factors affecting GVHD. (A) Acute GVHD incidence by age. (B) Chronic GVHD incidence by age. (C) Acute GVHD incidence by GVHD prophylaxis. (D) Chronic GVHD incidence by GVHD prophylaxis. The shaded regions indicate the corresponding 95% CIs. Reported *P* values are based on Gray's test. Of 116 patients who received CNI + other, 50 (43%) received alemtuzumab-based conditioning.

data on response or survival after 2 or more courses of IST among older patients, although a retrospective EBMT study found that repeat courses of IST had no significant impact on survival [7]. Additionally, MDS/AML and solid tumors may occur in 15% and 11% of patients, respectively, at 10 years after IST, and multiple courses of ATG increase the risk of developing MDS/AML [11,21,22].

Others have used cyclosporine as monotherapy, but response rates are lower than with the addition of ATG [23,24]. The use of eltrombopag for refractory SAA has improved response rates to 40%, but the early risk of clonal cytogenetic abnormality is 19% (median time to cytogenetic abnormality was 3 months), and monosomy 7 was the most common [12]. Taken together, in fit older patients with a suitable HLA-matched sibling or unrelated donor, transplantation after failure of 1 course of IST may be an alternative treatment option. Long-term survival after HCT for SAA is excellent, and the predominant cause of late mortality was GVHD-associated death, which in the recent era may be mitigated with alemtuzumab-containing regimens [17,18].

The incidence of and indication for allogeneic HCT in older patients with hematologic disorders are increasing worldwide [25], concurrent with improved clinical outcomes, an increased risk of hematologic malignancies [26], and a rising aged population globally. This is mirrored by a steady increase in the number of transplants being performed for SAA over the last decade, especially unrelated donor HCT (Figure 3). The question as to whether patient age remains relevant has been recently debated for hematologic malignancies [27]. Although we failed to detect a significant difference in survival between those aged 50 to 64 and 65 years or older, this should be interpreted with caution because the latter group accounted for only 16% of transplantations in the current analyses.

A further consideration for any patient age group is that if HCT is deferred until after the development of MDS/AML, outcomes of HCT are inferior [28,29]. Before consideration of HCT in older patients with SAA and at time of diagnosis, it is important to exclude hypocellular MDS, which may frequently mimic SAA on morphologic grounds [30]. MDS is far more common than SAA in older patients, with a median age at

Table 3
Risk Factors for Acute and Chronic GVHD

| Risk Factor	Subcategory	No. of Cases	No. of Events	sHR (95% CI)	P
	Acute GVHD				
	Total	404	95		
Registry	EBMT	229	36		
	CIBMTR	175	59	2.39 (1.55-3.67)	<.001
Age	50-64 yr	337	71		
	≥65 yr	67	24	1.7 (1.07-2.72)	.026
Patient sex	Male	208	52		
	Female	196	43	.86 (.56-1.32)	.49
Performance score	<90%	180	41		
	90-100%	224	54	1.2 (.78-1.85)	.41
GVHD prophylaxis	CNI + MMF	96	32		
	CNI + MTX	210	47	.69 (.43-1.11)	.13
	Other	98	16	.54 (.29-1.01)	.054
Regimen	Non-TBI regimen	303	62		
	TBI regimen	101	33	.96 (.55-1.67)	.87
Donor	Identical sibling	209	35		
	Unrelated donor	195	60	2.01 (1.18-3.42)	.011
Graft source	Bone marrow	220	53		
	Peripheral blood	184	42	.94 (.62-1.42)	.78
Interval from diagnosis to treatment, yr		404		1.06 (1-1.12)	.033
	Chronic GVHD				
	Total	315	98		
Registry	EBMT	143	38		
	CIBMTR	172	60	1.3 (.85-2.01)	.23
Age	50-64 yr	261	77		
	≥65 yr	54	21	1.2 (.74-1.97)	.46
Patient sex	Male	155	54		
	Female	160	44	.84 (.56-1.26)	.4
Performance score	<90%	142	42		
	90-100%	173	56	1.11 (.72-1.7)	.64
GvHD prophylaxis	CNI + MMF	76	38		
	CNI + MTX	166	48	.52 (.33-.81)	.004
	Other	73	12	.27 (.14-.53)	<.001
Regimen	Non-TBI regimen	229	70		
	TBI regimen	86	28	.94 (.51-1.75)	.85
Donor	Identical sibling	158	47		
	Unrelated donor	157	51	1.11 (.65-1.88)	.71
Graft source	Bone marrow	179	49		
	Peripheral blood	136	49	1.31 (.85-2)	.22
Interval from diagnosis to treatment, yr		315		1.03 (.96-1.1)	.46
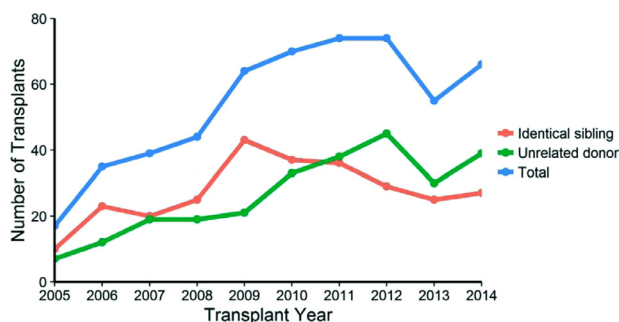
Figure 3. Number of transplants performed each year of the study by donor type: HLA-identical sibling and unrelated donor.

onset of MDS of 62 years. A diagnosis of MDS instead of SAA would impact the choice of conditioning regimen for HCT. Metaphase cytogenetics may not be discriminating, because up to 12% of SAA patients have an abnormal cytogenetic clone at diagnosis [31]. Even the presence of an acquired somatic mutation that is recurrent for MDS/AML such as ASXL1 or DNMT3A does not necessarily prove a diagnosis of hypocellular MDS instead of SAA, because small clones can be found in some SAA patients [10,32] as well as in normal older individuals as part of age-related clonal hematopoiesis [33-35].

We conclude that HCT deserves consideration as an option in older patients with SAA who have failed first-line IST. Better survival in patients with good performance score emphasizes the critical importance of preassessment of patients in terms of comorbidities. This will aid discussions with the patient about a potentially curative disease approach rather than disease-free survival associated with nontransplant options.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.08.029.

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