Current outcome of HLA identical sibling versus unrelated donor transplants in severe aplastic anemia: an EBMT analysis

Andrea Bacigalupo,[1] Gerard Socié,[2] Rose Marie Hamladji,[3] Mahmoud Aljurf,[4] Alexei Maschan,[5] Slawomira Kyrcz-Krzemien,[6] Alicja Cybicka,[7] Henrik Sengelov,[8] Ali Unal,[9] Dietrich Beelen,[10] Anna Locasciulli,[11] Carlo Dufour,[12] Jakob R. Passweg,[13] Rosi Oneto,[1] Alessio Signori[14] and Judith C.W. Marsh;[15] for the Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT)

[1]Divisione Ematologia e Trapianti di Midollo Osseo, IRCCS AOU San Martino-IST, Genova, Italy; [2]Hôpital Saint-Louis, Department of Hematology-BMT, Paris Cedex 10, France; [3]Centre Pierre et Marie Curie, Service Hématologie Greffe de Moëlle, Alger, Algeria; [4]King Faisal Specialist Hospital and Research Center, Oncology (Section of Adult Haematolgy/BMT), Riyadh, Saudi Arabia; [5]Federal Research Center for Pediatric Hematology, Oncology and Immunology, Moscow, Russia; [6]Medical University of Silesia, University Department Haematology and BMT, Katowice, Poland; [7]Wroclaw Medical University, Department of Children Hematology and Oncology, Bujwida Wroclaw, Poland; [8]Rigshospitalet, BMT Unit Department of Hematology L 4042, Department of Bone Marrow Transplantation, University Hospital, Copenhagen, Denmark; [9]Erciyes Medical School, Dept. of Hematology–Oncology, Kapadokya, BMT Center, Kayseri, Turkey; [10]Department of Bone Marrow Transplantation, University Hospital, Essen, Germany; [11]Ospedale S. Camillo, Haematology and SCT Unit, Padiglione Cesalpino Circonvallazione, Rome, Italy; [12]Institute G. Gaslini, Genova, Italy; [13]University Hospital, Hematology, Basel, Switzerland; [14]Department of Health Science, Medical Statistics, University of Genova, Italy; [15]GKT School of Medicine, Deptartment of Haematological Medicine, King's Denmark Hill Campus, London, UK

ABSTRACT

We have analyzed 1448 patients with acquired aplastic anemia grafted between 2005 and 2009, and compared outcome of identical sibling (n=940) *versus* unrelated donor (n=508) transplants. When compared to the latter, sibling transplants were less likely to be performed beyond 180 days from diagnosis (39% *vs.* 85%), to have a cytomegalovirus negative donor/recipient status (15% *vs.* 23%), to receive antithymocyte globulin in the conditioning (52% *vs.* 61%), and more frequently received marrow as a stem cell source (60% *vs.* 52%). Unrelated donor grafts had significantly more acute grade II-IV (25% *vs.* 13%) and significantly more chronic graft-versus-host disease (26% *vs.* 14%). In multivariate analysis, the risk of death of unrelated donor grafts was higher, but not significantly higher, compared to a sibling donor (P=0.16). The strongest negative predictor of survival was the use of peripheral blood as a stem cell source (P<0.00001), followed by an interval of diagnosis to transplant of 180 days or more (P=0.0005), patient age 20 years or over (P=0.0005), no antithymocyte globulin in the conditioning (P=0.003), and donor/recipient cytomegalovirus sero-status, other than negative/negative (P=0.04). In conclusion, in multivariate analysis, the outcome of unrelated donor transplants for acquired aplastic anemia, is currently not statistically inferior when compared to sibling transplants, although patients are at greater risk of acute and chronic graft-*versus*-host disease. The use of peripheral blood grafts remains the strongest negative predictor of survival.

Introduction

The current standard of care for patients with acquired severe aplastic anemia (SAA) who lack an HLA identical sibling (SIB) calls for a course of immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and cyclosporine.[1] Transplantation from an unrelated donor (UD) is usually considered after failure of at least one course of IST.[2] This strategy is based on a relatively high risk of complications for UD transplant recipients, such as graft rejection, graft-*versus*-host disease (GvHD) and infections.[3-5] However, things have changed in recent years, and the outcome of unrelated donor transplants has significantly improved.[6-8]

This is probably the consequence of better selection of donors by allele matching, changes in the conditioning regimens with the use of fludarabine, with or without low-dose total body irradiation (TBI),[9-11] and improved supportive care, including better diagnosis and treatment of transplant-related infections. Improved supportive care has benefited also SIB transplants, although to a lesser extent than UD transplants;[12] this is because the outcome of SIB transplants was already extremely good, especially, but not exclusively,[13] in young patients.[14-15]

Therefore, improved survival is currently seen with both UD and SIB transplant, and the question is how do they compare, this being relevant for treatment strategies in patients with acquired SAA. To answer this question, we have examined the outcome of 1448 patients with SAA undergoing an UD or an SIB transplant between 2005 and 2009, and reported to the SAA registry of the EBMT.

Methods

Patients

Patients had been reported to the Registry of the Working Party on Severe Aplastic Anemia (WPSAA) of the European Group for Blood

 doi:10.3324/haematol.2014.115345
Manuscript received on August 7, 2014. Manuscript accepted on January 21, 2015.
Correspondence: andrea.bacigalupo@hsanmartino.it

Table 1. Clinical characteristics of 1448 patients.

Donor type	Sibling	Unrelated	Missing	P
N	940	508		
Age >20 years	474 (50%)	272 (53%)	(–)	0.2
Female donor in male recipient	237 (25%)	62 (12%)	(–)	<0.001
Interval DxTx >180 days	369 (39%)	432 (85%)	(–)	<0.001
CMV sero-status (D-/R-)	140 (15%)	115 (23%)	(36)	<0.001
ATG in the conditioning	484 (52%)	311 (61%)	(2)	0.0003
Fludarabine-based regimen	144 (20%)	205 (62%)	(–)	<0.001
Radiation in the conditioning	31 (4%)	107 (32%)	(–)	<0.001
Stem cell source (BM)	566 (60%)	265 (52%)	(–)	0.003
FU days median	1157 (1-3270)	1143 (2-3324)	(–) (–)	0.07

DxTx: interval diagnosis transplant; CMV sero-status (D-/R-): number and percentage of pairs who were cytomegalovirus donor-negative/recipient-negative; ATG: antithymocyte globulin; BM: bone marrow; FU: follow up.

and Marrow Transplantation (EBMT), and the database resides in the Department of Medical Statistics of the University of Leiden, The Netherlands. The data manager for the Registry is a co-author (RO). The quality of the data are assured by external audits, performed by EBMT and the Joint Accreditation Committee of the International Society of Cell Therapy (ISCT) and EBMT (JACIE). Eligibility criteria were: 1) a diagnosis of acquired SAA; 2) first transplant between 2005-2009; 3) bone marrow (BM) or peripheral blood (PB) as a stem cell source; and 4) matched sibling or matched unrelated as a donor type. Exclusion criteria were cord blood transplants and mismatched family donors.

HLA matching was defined by the transplant center as matched or mismatched. This study excluded mismatched grafts, but 8/8 HLA matched could not be differentiated from 10/10 matched donors. It is also presumed that allele matching was applied, these transplants having been performed in the period 2005-2009. The patients were treated in 290 centers (*see Online Supplementary Appendix*).

Unrelated and sibling transplants

Clinical characteristics of UD and SIB transplants are shown in Table 1. There were significant differences between SIB and UD grafts. The latter had less female donor to male recipients (P<0.001), twice as many patients who were grafted beyond six months from diagnosis (P<0.001), more CMV negative donor/recipient pairs (P<0.001), more patients receiving *in vivo* T-cell depletion with ATG (P<0.001), more patients receiving radiation- or fludarabine-based conditioning regimens (P<0.001), and less patients receiving marrow as a stem cell source (P=0.003). It should be noted that radiation in the UD setting is currently limited to low-dose radiation (such as 2 or 3 Gy), but details on radiation doses were not collected in this data set. There was no statistical difference in median length of follow up (P=0.07) (Table 1).

Statistical analysis

Analyses were performed with the Stata software (StataCorp, v.11). Comparisons between transplant groups were carried out using the χ^2 test for categorical variables and the non-parametric Mann-Whitney test for continuous variables. The end point for survival analysis was death due to any cause.

Univariate and multivariate survival analyses were carried out using the Cox proportional hazard model. All significant variables among those assessed in univariate analysis were considered for the multivariate model. Actuarial survival according to donor type (SIB and UD) was also calculated after stratification of patients into 3 risk categories: the risk score was derived by adding up the Hazard Ratio (HR) of each negative predictor selected in multivariate analysis (stem cell source, interval diagnosis to transplant, age, use of ATG, and CMV status). The 25 and 75 percentiles were 3 and 6. The patients were thus divided into 3 groups: a low-risk group (score 0-3; n=391), an intermediate-risk group (score 3-6; n=709), and high-risk group (score >6; n=348).

Table 2. Outcome of HLA identical sibling and unrelated donor grafts.

Source N.	Sibling 940	Unrelated 508	P
Engraftment	91%	91%	0.9
Acute GvHD II-IV	13%	25%	<0.0001
Acute GvHD III-IV	5%	10%	<0.0001
Chronic GvHD	14%	26%	<0.0001
Extensive chronic GvHD	6%	11%	0.002
Patients surviving	777 (83%)	384 (76%)	
Deceased n /%	163 (17%)	124 (24%)	
Causes of death*			
GvHD	37 (3.9%)	34 (6.7%)	
Interstitial pneumonia	1 (0.1%)	7 (0,4%)	
Other lung complications	13 (1.4%)	4 (0.8%)	
Infections	85 (9%)	58 (11.4%)	
Rejection	14 (1.5%)	11 (2.2%)	
Hemorrhage	12 (1.3%)	11 (2.2%)	
VOD	8 (0.9%)	3 (0.6%)	

*GvHD: graft-versus-host disease; VOD: veno-occlusive disease. *The sum of the different causes of death exceeds 100% because they represent primary and secondary causes of death.*

Results

Engraftment and graft-versus-host disease

The cumulative incidence (CI) of engraftment, as identified by a neutrophil count of 0.5x10^9/L, was 91% for both SIB and UD transplants; median time to neutrophil

engraftment was 19 days for SIB (3-75) and 18 days (3-89) for UD (Table 2). The CI of grade II-IV acute GvHD was 13% in SIB grafts (95% CI: 11%-15%) and 25% in UD grafts (95% CI: 21%-29%); *P*<0.0001) (Figure 1A); the CI of acute GvHD grade III-IV was 5% *versus* 10%, respectively (*P*<0.0001). The CI of chronic GvHD was 14% in SIB grafts (95% CI: 12%-18%) and 26% in UD grafts (95% CI: 22%-31%) (*P*<0.0001) Figure 1B).

Causes of death in patients receiving SIB or UD grafts are outlined in Table 2; there is a slight excess of deaths due to GvHD, interstitial pneumonia, and infections in patients receiving UD grafts while deaths due to rejections were comparable.

Univariate analysis of survival

A total of 287 deaths were registered. At three months survival was 89% (SE=0.8%), at six months 86% (SE=0.9%), at one year 83% (SE=1%), and at two, three and five years 80% (SE=1.1%), 79% (SE=1.1%) and 78% (SE=1.2%), respectively.

The use of PB as a stem cell source resulted in significantly inferior outcome (70%, SE=2%) as compared to BM (83%, SE=1.6%); *P*<0.001) (Figure 2A). Survival in patients under the age of 20 years was superior to survival in older patients (84%, SE=1.6% *vs.* 72%, SE=1.9%; *P*<0.00001) (Figure 2B). There was an advantage for patients grafted within six months from diagnosis (85%, SE=1.6%) *versus* patients grafted later (72%-SE=1.9%) (*P*<0.00001) (Figure 2C) and for patients receiving ATG in the conditioning regimen (81%, SE=1.8%) *versus* patients

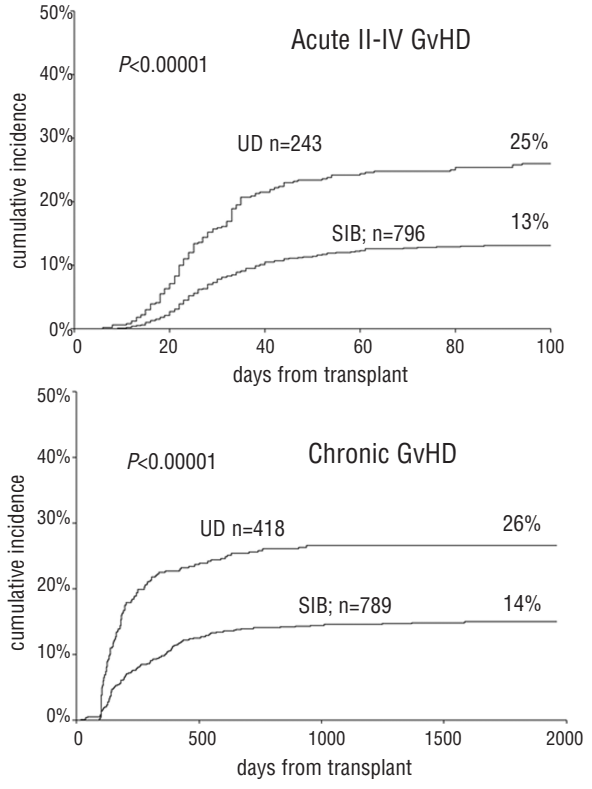

Figure 1. Cumulative incidence of acute (A) and chronic (B) graft-*versus*-host disease (GvHD): a higher rate is seen for both in patients grafted from unrelated as compared to HLA identical sibling donors.

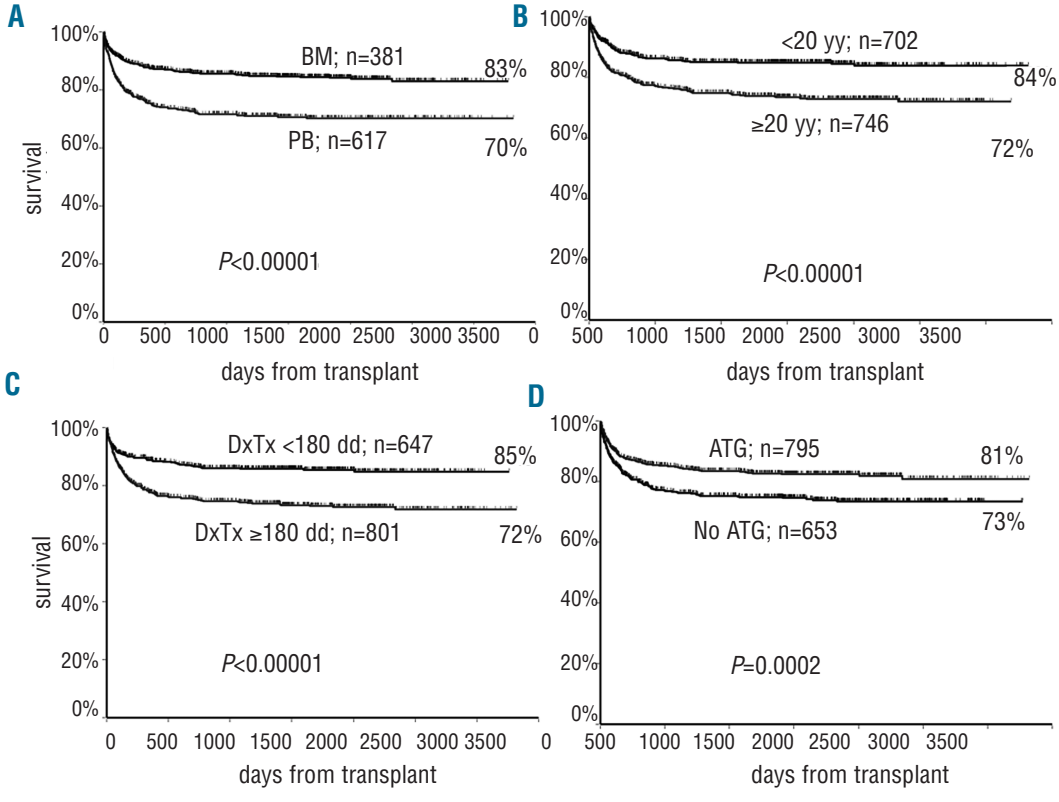

Figure 2. Univariate analysis of survival in patients with acquired aplastic anemia stratified for stem cell source, (BM: bone marrow; PB: peripheral blood) (A) age </>20 years (B), interval between diagnosis transplant (DxTx) </>180 days (d), (C) and use of antithymocyte globulin (ATG) in the conditioning regimen (D).

not receiving ATG (73%, SE=1.9%) (P<0.0002) (Figure 2D), as well as for CMV negative donor/recipient pairs (82%, SE=2.9%) *versus* other CMV donor recipient combinations (76%, SE=1.4%) (P=0.02) (*survival data not shown*).

In univariate analysis, radiation-based regimens (P=0.09), fludarabine-based regimen (P=0.1), and female donors to male recipients (P=0.2) were not significant predictors (Table 3).

Table 3. Univariate and multivariate Cox analysis on survival.

Base-line value	Compared value	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
Donor type		0.003		0.16	
SIB	UD	1.43 (1.13–1.80)		1.2 (0.93–1.55)	
Stem cell source			< 0.001		< 0.001
BM	PB	2.04 (1.62–2.58)		1.66 (1.31–2.12)	
Interval diagnosis transplant			< 0.001		< 0.001
< 180 dd	≥ 180 dd	1.95 (1.52–2.51)		1.63 (1.24–2.15)	
Age			< 0.001		0.001
< 20 years	≥ 20 years	1.82 (1.43–2.32)		1.54 (1.20–1.98)	
ATG in the conditioning regimen			< 0.001		0.003
Yes	No	1.53 (1.21–1.93)		1.43 (1.13–1.81)	
CMV donor /recip sero-status			0.02		0.04
D-/R-	Other	1.50 (1.06–2.11)		1.43 (1.01–2.02)	
Fludarabine-based regimen			0.1		
No	Yes	1.17 (0.87–1.57)			
Radiation-based regimen			0.09		
No	Yes	1.38 (0.95–1.99)			
Female to male recipient			0.2		
No	Yes	1.19 (0.87–1.61)			

HR: hazard ratio; SIB: HLA identical sibling; UD: unrelated donor; BM: bone marrow; PB: peripheral blood; ATG: antithymocyte globulin; CMV: cytomegalovirus; D/R donor recipient (recip) CMV sero-status.

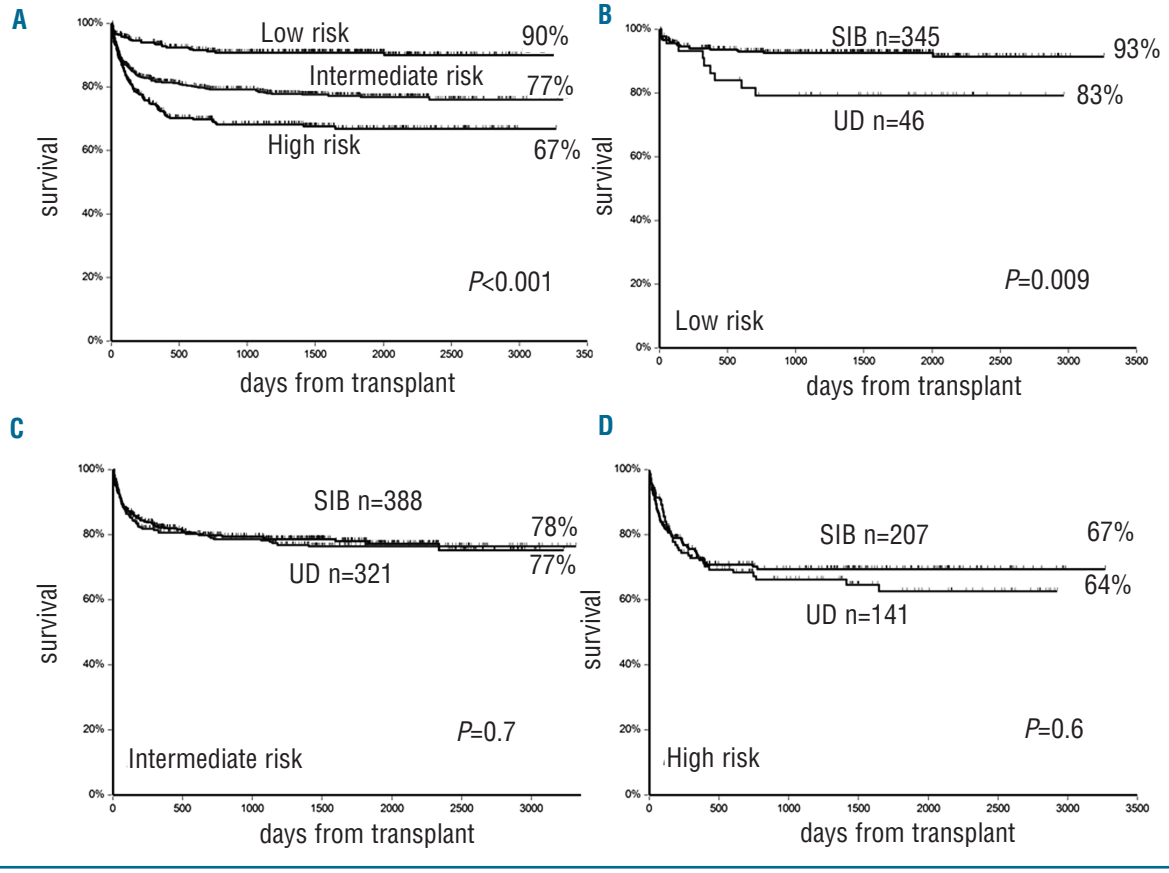

Figure 3. Survival of patients stratified into 3 risk groups according to prognostic variables (stem cell source, interval diagnosis transplant, age, use of antithymocyte globulin (ATG) and cytomegalovirus (CMV) status): low risk, intermediate risk, and high risk (A). The effect of donor type (UD *vs.* SIB) is significant in low-risk patients (B); there is no statistical difference between intermediate-risk (C) and high-risk patients (D).

Table 4. Univariate and multivariate Cox analysis on survival stratified according to donor type.

		Multivariate				
		SIB (n=940)		UD (n=508)		Difference in SIB /UD (*P*)*
Base-line value	Compared value	HR (95% CI)	*P*	HR (95% CI)	*P*	
Stem cell source			0.001		0.038	0.26
BM	PB	1.75 (1.26 – 2.42)		1.47 (1.02–2.12)		
Interval diagnosis transplant			<0.001		0.85	0.013
<180 dd	≥180 dd	1.94 (1.41 – 2.67)		0.95 (0.59–1.54)		
Age		0.01			0.047	0.33
<20 years	≥0 years	1.56 (1.11 – 2.19)		1.45 (1.01–2.10)		
ATG in the conditioning regimen			0.013		0.068	0.33
YES	NO	1.50 (1.09 – 2.07)		1.39 (0.98–1.99)		
CMV donor /recip. sero status			0.40		0.067	0.32
D-/R-	Other	1.25 (0.75 – 2.08)		1.56 (0.97–2.49)		
Donor type		–		–		
SIB	UD					

*SIB: HLA identical sibling; UD: unrelated donor; HR: hazard ratio; BM: bone marrow; PB: peripheral blood; ATG: antithymocyte globulin; CMV: cytomegalovirus; D-/R-: donor recipient CMV sero-status. *Test on the interaction between donor type and each one of the clinical characteristics to assess if the adjusted impact of each characteristic on the outcome differs between SIB and UD donors.*

Multivariate analysis

Finally, we entered the 5 negative predictors together with donor type in a multivariate Cox model (Table 3). The strongest negative predictors of survival was the use of PB as a stem cell source [HR=1.66 (1.31-2.12); *P*<0.001], followed by an interval diagnosis to transplant (Dx-Tx) of 180 days or more [HR=1.63 (1.24-2.15); *P*<0.001], patient age 20 years or more [HR=1.54 (1.20-1.98); *P*=0.001], no antithymocyte globulin (ATG) in the conditioning [HR=1.43 (1.13-1.81); *P*=0.003], and CMV donor/recipient sero-status other than negative [HR=1.43 (1.01-2.02); *P*=0.04]. The use of an UD as compared to an SIB was not a statistically significant predictor [HR=1.2 (0.93-1.55); *P*=0.16] (Table 3).

We then ran a multivariate analysis separately in patients receiving SIB or UD grafts (Table 4). We show that all predictors had the same effect in SIB and UD patients, with one exception: the interval diagnosis to transplant. This was highly significant in SIB (*P*<0.001) but not in UD grafts (*P*=0.8), possibly due to a selection bias for very severe patients receiving an early UD graft (Table 4).

Risk score

Survival of patients stratified into three risk categories, as described in the Methods section, is shown in Figure 3A: low-risk (n=391) 90%, intermediate-risk (n=709) 77%, and high-risk (n=348) 67%. We then looked at the effect of donor type (SIB, UD) in the 3 groups: there is a significant survival advantage for SIB grafts in low-risk patients (Figure 3B), although the number of UD patients is small (n=46). There is a possibility that this small group represented a selection of patients with very severe aplasia; indeed, mortality was 40% for patients grafted within 90 days from diagnosis, 18% for grafts between 91 and 180 days, and 15% for transplants beyond 180 days.

In the large intermediate-risk group, comprising 50% of the entire patient population, actuarial survival is superimposable (Figure 3C). There is no significant survival difference in the smaller high-risk group (Figure 3D).

Discussion

We have shown in the current study that the outcome of matched UD transplant for acquired SAA is not statistically inferior to SIB transplants, in multivariate analysis, when corrected for patient age, interval diagnosis to transplant, stem cell source, the use of ATG, and donor recipient CMV status. Patients undergoing UD grafts, however, remain at greater risk of acute and chronic GvHD, and this study has not assessed the quality of life of these patients, which may be significantly affected, especially by chronic GvHD. We have also confirmed several predictors of outcome, some of which can be modified, such as the stem cell source and *in vivo* T-cell depletion, and others which cannot be changed, such as patient age.

The role of ATG in the conditioning regimen, although historically often used in SAA to prevent rejection, is controversial, and in a prospective randomized trial, ATG has failed to show a superiority over controls.[16] However, this could be due to a question of numbers, since the survival advantage for ATG in that trial (134 patients) was 6%, and it is 8% in this series (1448 cases), being predictive in both univariate and multivariate analysis. In addition, interval diagnosis to transplant, age, CMV donor/recipient status, and stem cell source, all proved significant predictors, confirming well known data.[14] The effect of different conditioning regimens, TBI or fludarabine-based, did not prove significant in multivariate analysis.

Stem cell source has been studied both in sibling transplants[17,18] as well as in unrelated donor grafts,[19] including overall almost 3000 patients, and survival of BM grafts has always proved superior to G-CSF mobilized PB, with the exception of one study on a small number of children.[20] We confirm in the present series of 1448 cases, that PB as

stem cell source, when compared to BM, is the strongest negative predictor of survival, both for SIB and UD: when the two donor types are combined together, the actuarial 5-year survival is 83% for BM *versus* 70% for PB ($P<0.00001$), and death rate due to GvHD and infections is 7% for BM *versus* 17% for PB recipients ($P<0.0001$). When looking at the combined effect of stem cell source and donor type, the use of PB increased the risk of death in SIB patients from 23% to 37% and in UD patients from 29% to 39%. Therefore, bone marrow remains the stem cell source of choice in patients with acquired SAA undergoing a first allogeneic transplant, both from SIB as well as from UD. If at all possible, unrelated donors should be asked to give BM. BM harvest is a safe and well-established procedure, but if a donor refuses to give BM and there are multiple donor options, then donors only willing to give PB should be rejected in favor of those willing to give BM.

Age is a known predictor of survival and our study confirms this, with crude survival of 86%, 82%, 62% and 42%, respectively, in patients aged under 20, 21-40, 41-60 and over 60 years; in the latter small group (n=36), survival of SIB grafts was 57% *versus* 12% for 12 UD transplants. Interval diagnosis to transplant was the other very strong predictor, with an HR of 1.63 for patients grafted beyond six months from diagnosis. Because UD grafts are almost exclusively performed after a course of IS, most UD patients (85%) were grafted beyond six months from diagnosis. CMV donor recipient sero-status was another predictor, but again with a different distribution between SIB and UD patients. Because of these significant differences in clinical characteristics in the two groups, especially in terms of interval diagnosis to transplant, but also stem cell source and CMV status, a comparison of SIB and UD grafts can only be attempted in a multivariate analysis. In a Cox analysis, stem cell source, interval diagnosis to transplant, age, use of ATG and CMV status remained significant predictors, whereas donor type (SIB *vs.* UD) was not predictive ($P=0.16$).

The effect of donor type was also assessed in patients at different risk of death, low intermediate and high, based on the presence of negative predictors and the Cox derived HRs. Survival of UD grafts was inferior to SIB transplants, in the low-risk group, but not in the intermediate- and high-risk group. This may reflect a selection bias for patients in the low-risk group. In other words, younger patients grafted earlier in the course of their disease, may have had a very severe disease, and therefore may have forced early transplant strategies. In keeping with this hypothesis is the fact that mortality was highest in patients grafted within 90 days from diagnosis, and declined thereafter. Therefore, comparison of SIB-UD in the low-risk group is probably between elective early SIB transplants and forced early UD transplants.

The recently published guidelines of the EBMT still read "standard front-line treatment for acquired SAA patients who do not have an HLA identical sibling is combined immunosuppressive therapy, with ATG and cyclosporine".[1] Whether an UD graft may be considered first-line therapy in young patients with very severe aplasia should be tested within a clinical trial, also considering the significant increased risk of acute and chronic GvHD in UD graft recipients.

In conclusion, we believe this study suggests improved outcome of UD grafts for acquired aplastic anemia in recent years, not statistically inferior to SIB grafts, when corrected for confounding variables, and especially time to transplant. This information warrants the early activation of an unrelated donor search for patients lacking an HLA-matched sibling. Once an UD has been identified, whether to proceed to an UD transplant will depend on other considerations, such as the degree of matching between the potential donor and the recipient, and the patient's age, blood counts, transfusion requirement, and performance status. The significant increased risk of acute, and especially chronic, GvHD in UD transplants needs to be carefully addressed in prospective national or international studies. One study comparing the use of ATG and alemtuzumab in the conditioning is being planned within the EBMT.

Funding

This study was supported by EBMT and Fondazione Ricerca Trapianto Midollo Osseo (FARITMO) Genova, Italy. AS is a PhD at the Department of Health Science, Medical Statistics, University of Genova, Genova, Italy

Authorship and Disclosures

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.

References

1. Dufour C, Svahn J, Bacigalupo A, on behalf of the Severe Aplastic Anemia-Working Party of the EBMT. Front-line immunosuppressive treatment of acquired aplastic anemia. Bone Marrow Transplant. 2013;48(2):174-177.
2. Bacigalupo A, Marsh JC. Unrelated donor search and unrelated donor transplantation in the adult aplastic anaemia patient aged 18-40 years without an HLA-identical sibling and failing immunosuppression. Bone Marrow Transplant. 2013;48(2):198-200.
3. Deeg HJ, Amylon ID, Harris RE, et al. Marrow transplants from unrelated donors for patients with aplastic anemia: minimum effective dose of total body irradiation. Biol Blood Marrow Transplant. 2001;7(4):208-215.
4. Kojima S, Matsuyama T, Kato S, et al. Outcome of 154 patients with severe aplastic anemia who received transplants from unrelated donors: the Japan Marrow Donor Program. Blood. 2002;100(3):799-803.
5. Bacigalupo A, Locatelli F, Lanino E, et al. Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation. Fludarabine, cyclophosphamide and anti-thymocyte globulin for alternative donor transplants in acquired severe aplastic anemia: a report from the EBMT-SAA Working Party. Bone Marrow Transplant. 2005;36(11):947-950.
6. Maury S, Balere-Appert ML, Chir Z, et al. French Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC). Unrelated stem cell transplantation for severe acquired aplastic anemia: improved outcome in the era of high-resolution HLA matching between donor and recipient. Haematologica. 2007;92(5):589-596.
7. Viollier R, Socié G, Tichelli A, et al. Recent improvement in outcome of unrelated donor transplantation for aplastic anemia. Bone Marrow Transplant. 2008;41(1):45-50.
8. Kennedy-Nasser AA, Leung KS, Mahajan

A, et al. Comparable outcomes of matched-related and alternative donor stem cell transplantation for pediatric severe aplastic anemia. Biol Blood Marrow Transplant 2006;12(12):1277-1284.
9. Bacigalupo A, Socie' G, Lanino E, et al; Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation. Fludarabine, cyclophosphamide, antithymocyte globulin, with or without low dose total body irradiation, for alternative donor transplants, in acquired severe aplastic anemia: a retrospective study from the EBMT-SAA working party. Haematologica. 2010;95(6):976-982.
10. Marsh JC, Gupta V, Lim Z, et al. Alemtuzumab with fludarabine and cyclophosphamide reduces chronic graft versus host disease after allogeneic stem cell transplantation for acquired aplastic anemia Blood. 2011;118(8):2351-2357.
11. Samarasinghe S, Steward C, Hiwarkar P, et al. Excellent outcome of matched unrelated donor transplantation in paediatric aplastic anaemia following failure with immunosuppressive therapy: a United Kingdom multicentre retrospective experience. Br J Haematol. 2012;157(3):339-346.
12. Locasciulli A, Oneto R, Bacigalupo A, et al on behalf of the Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (SAA-WP, BMT). Outcome of patients with acquired aplastic anemia given first line bone marrow transplantation or immunosuppressive treatment in the last decade: a report from the European Group for Blood and Marrow Transplantation (EBMT). Haematologica. 2007;92(1):11-18.
13. Sangiolo D, Storb R, Deeg HJ, et al. Outcome of allogeneic hematopoietic cell transplantation from HLA-identical siblings for severe aplastic anemia in patients over 40 years of age. Biol Blood Marrow Transplant. 2010;16(10):1411-1418.
14. Gupta V, Eapen M, Brazauskas R, et al. Impact of age on outcomes after bone marrow transplantation for acquired aplastic anemia using HLA-matched sibling donors. Haematologica. 2010;95(12):2119-2125.
15. Sorror ML, Leisenring W, Deeg HJ, Martin PJ, Storb R. Twenty-year follow-up in patients with aplastic anemia given marrow grafts from HLA-identical siblings and randomized to receive methotrexate/cyclosporine or methotrexate alone for prevention of graft-versus-host disease. Biol Blood Marrow Transplant. 2005;11(7):567-568.
16. Champlin RE, Perez WS, Passweg JR, et al. Bone marrow transplantation for severe aplastic anemia: a randomized controlled study of conditioning regimens. Blood. 2007;109(10):4582-4585.
17. Schrezenmeier H, Passweg JR, Marsh JC, et al. Worse outcome and more chronic GVHD with peripheral blood progenitor cells than bone marrow in HLA-matched sibling donor transplants for young patients with severe acquired aplastic anemia. Blood. 2007;110(4):1397-1400.
18. Bacigalupo A, Socié G, Schrezenmeier H, et al for the Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT). Bone marrow versus peripheral blood matched sibling transplants, in acquired aplastic anemia: survival advantage for marrow in all age groups. Haematologica, 2012;97(8):1142-1148.
19. Eapen M, Le Rademacher J, Antin JH, et al. Effect of stem cell source on outcomes after unrelated donor transplantation in severe aplastic anemia. Blood. 2011;118(9):2618-2621.
20. Chen J, Lee V, Luo CJ, et al. Allogeneic stem cell transplantation for children with acquired severe aplastic anaemia: a retrospective study by the Viva-Asia Blood and Marrow Transplantation Group. Br J Haematol. 2013;162(3):383-391.