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ORIGINAL ARTICLE

Recent improvement in outcome of unrelated donor transplantation for aplastic anemia

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The aim was to determine whether outcome of unrelated donor transplantation for severe aplastic anemia has improved in recent years and whether this is due to patient selection or better transplant technology. We analyzed 498 patients transplanted during 1990–2005. By running univariate regression models dichotomizing year of transplantation we defined 1998 as the year of the most significant change in survival. Five-year survival increased from 32±8% before 1998 to 57±8% after 1998 ($P<0.0001$). When comparing the cohort before ($n=149$) and after 1998 ($n=349$), there were no differences except for older age, and more frequent use of PBSCs, after 1998. High-resolution HLA typing data were unavailable. After 1998, there was less graft failure (11 vs 26%, $P<0.0001$), less acute GvHD (cumulative incidence 28 vs 37%, $P=0.02$) and less chronic GvHD (22 vs 38%, $P=0.004$). In multivariate analyses adjusting for differences in age, HLA-mismatch, performance score and time to transplantation, there was no change in the year of transplant effect (relative risk of death in transplants after 1998: 0.44 (95% confidence interval 0.33–0.59)). There is no evidence for patient selection to explain significantly improved survival in patients transplanted after 1998. We speculate that this is due to better donor matching.

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Introduction

BMT from an HLA-identical sibling is an established treatment for young patients with acquired severe aplastic anemia (SAA).[1–5] For patients without an HLA-matched related donor, immunosuppressive treatment with antithymocyte globulin and cyclosporine is an alternative.[6–9] Both treatment modalities may result in prolonged disease-free survival. Younger patients with severe neutropenia have better outcomes using an up-front transplant strategy.[8] For patients failing immunosuppressive therapy with a suitable alternative donor, referral for transplantation should be considered.[10] Successful transplantation with donors other than HLA-identical relatives has been reported for many years.[11–17] Probabilities of long-term survival after unrelated donor transplantation of SAA in earlier studies ranged from 29 to 50%.[17–20] In the past, unrelated donor transplantation has generally been recommended for younger patients, and only after they have failed at least two courses of immunosuppressive treatment.

Because of an impression of improved outcome in more recently transplanted patients with unrelated donors, we wished to address the following questions: (1) whether such an improvement could be confirmed by analyzing a large number of patients; (2) the best time point defining this change; (3) how cohorts before and after this time point were compared; and (4) whether explanatory factors relating to patient selection or transplant technology were associated with this improvement.

Patients and methods

The European Group for Blood and Marrow Transplantation is a voluntary working group of more than 450 transplant centers allowing scientists and physicians involved in BMT to share experience and develop cooperative studies. Participating centers are required to report a minimal data set, to provide yearly follow-up on all consecutive transplants and are also encouraged to report a more complete data set. For this study, we considered all patients (that is, those with complete information and those with minimal essential data only) receiving an unrelated donor transplant for acquired SAA between 1990 and 2005 reported by 142 transplant teams. The median number of patients per team was 2, with a range of 1–27. Median follow-up of surviving patients was 86 (15–152) months in patients transplanted in 1990–1998 and 13 (3–83) months in patients transplanted after 1998.

This study included 498 patients. To analyze whether improvement in outcome had occurred and at what point of time, we ran repeated univariate proportional hazard regression models dichotomizing year of transplantation between recent and older transplants. We found that cohorts transplanted before and after 1998 (1 January) most significantly differed in outcome. Five-year survival ($\pm$95% confidence interval) increased from 32$\pm$8% for patients transplanted before 1998 to 57$\pm$8% for those transplanted after 1998 ($P<0.0001$).

There were 149 patients (gender: 89 (58%) male; median age: 16.9 years (range: 1–48)) transplanted before 1998 and 349 patients (gender: 202 (58%) male; median age: 18.6 years (1–65)) transplanted after 1998 ($P=0.54$ for gender and $P=0.08$ for age). Comparison of patients transplanted before and after 1998 is shown in Table 1.

The cohorts did not differ in age, gender, performance score, time interval between diagnosis and transplantation, donor age or HLA matching based on serology for class I and low-resolution DNA testing for class II. HLA high-resolution typing data were available for only a small minority of patients and this information was therefore not used. The cohorts differed in the source of stem cells (more peripheral blood after 1998) and in some conditioning regimens (more use of fludarabine and less TBI after 1998). Younger patients had a shorter waiting time until transplantation than older patients irrespective of the year of transplant. The proportion of patients with missing information on important variables is shown in Table 1.

There was no precise information on the proportion of patients failing immunosuppressive treatment prior to unrelated donor transplantation. Information was available for half of the patients but the database did not allow us to separate those without treatment from those with missing information. The median time interval between diagnosis and transplantation was 14 months for both groups, that is, those with prior immunosuppressive treatment and those with missing information, and it is likely that the majority of patients had failed at least one course immunosuppressive treatment.

Outcomes analyzed were overall survival, graft failure, acute and chronic GvHD. Acute GvHD was defined as grade II–IV, and patients with >20 days survival being at risk. Chronic GvHD was defined as any grade of chronic GvHD (limited and extensive) in patients surviving >100 days. Graft failure was defined as either primary non-engraftment or secondary graft failure. Patients were compared using the χ^2 test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Cumulative incidence was used for acute GvHD, and the Kaplan–Meier estimator for overall survival. The proportion of patients with graft failure and with chronic GvHD were compared. To find causes for the improvement in survival, we compared a univariate Cox regression model

Table 1 Patient characteristics

	Before 1998	*After 1998*	P
N	149	349	
Age, median (range)	16.9 (1–48)	18.6 (1–65)	0.08
Gender male *n* (%)	89 (58%)	202 (58%)	0.54
Waiting time diagnosis–transplant (months)			0.46
<6	24 (16%)	43 (12%)	
6–12	37 (25%)	94 (27%)	
12–24	39 (26%)	88 (25%)	
>24	49 (33%)	124 (36%)	
Median (months, range)	14.3 (3–167)	15.8 (2–209)	0.18
Karnofsky performance status			0.13
Good (80–100)	39 (26%)	190 (55%)	
Poor (0–70)	2 (1%)	32 (9%)	
Missing	108 (73%)	127 (36%)	
Stem cell source			<0.001
Bone marrow	145 (97%)	250 (72%)	
Peripheral blood	4 (3%)	99 (28%)	
Donor HLA match[a]			0.14
Unrelated matched	114 (77%)	287 (82%)	
Unrelated mismatched	35 (23%)	62 (28%)	
Donor–recipient sex match			
m→m	41 (28%)	138 (40%)	0.14
f→f	33 (22%)	60 (17%)	
f→m	37 (25%)	50 (14%)	
m→f	26 (17%)	76 (22%)	
Conditioning regimen			<0.001
Cyclophosphamide (Cy)	18 (12%)	13 (4%)	
Cy+ATG	4 (3%)	19 (5%)	
TBI+other	75 (50%)	110 (32%)	
Fludarabine+other	0	60 (17%)	
Busulfan+Cy	15 (10%)	23 (7%)	
Other	23 (15%)	29 (8%)	
Missing	14 (9%)	95 (27%)	
GvHD prophylaxis			0.12
Cyclosporin A (CSA)	36 (24%)	43 (12%)	
CSA+methotrexate	62 (42%)	119 (34%)	
ATG	6 (4%)	20 (6%)	
T-cell-depletion	2 (1%)	2 (1%)	
Other	1 (1%)	0	
Missing	42 (28%)	165 (47%)	
Donor age			
Median (range)	38.5 (0–62)	36.0 (0–63)	$P=0.509$

[a]HLA matching based on serology for class I and low-resolution DNA testing for class II.

with year of transplant (dichotomizing before and after 1998) to a full model with all other covariates after selecting significant covariates by a forward stepwise selection procedure.[21,22]

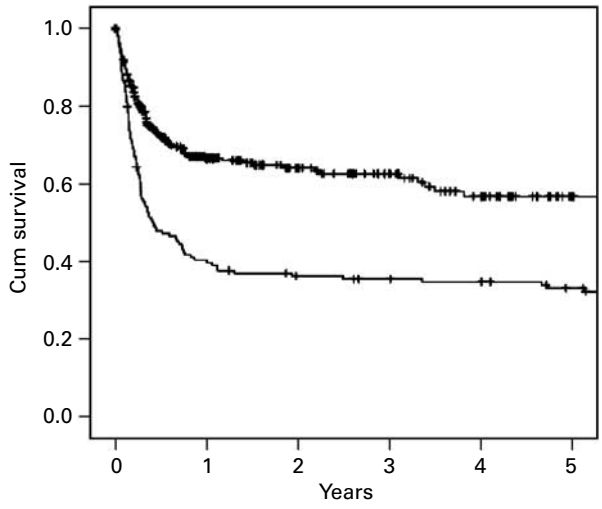

Figure 1 Five-year survival in recipients of unrelated donor transplants for severe aplastic anemia before and after 1998.

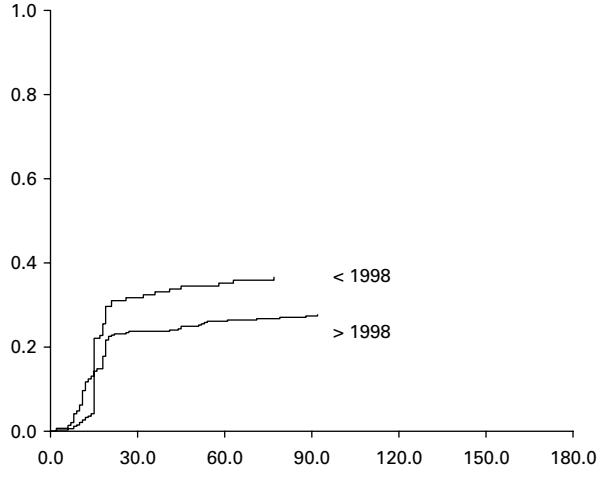

Figure 2 Cumulative incidence of grade II–IV acute GvHD in recipients of unrelated donor transplants for severe aplastic anemia before and after 1998.

Results

Figure 1 shows the survival curves of patients transplanted before and after 1998. Five-year survival was 32% (±8%) in the early and 57% (±8%), $P=0.0001$ in the late cohort. Survival probabilities also differed in patients receiving HLA low-resolution matched ($n=401$) vs mismatched ($n=97$) transplants, being 52% (±6%) in the matched group vs 34% (±14%) in the mismatched group ($P=0.005$). Improvement in survival was associated with less graft failure (primary and secondary), less acute GvHD (Figure 2) and less chronic GvHD in patients transplanted after 1998 as compared to patients transplanted before 1998 (Table 2).

Patients transplanted after 1998 had about half the risk of death (relative risk 0.47 (95% confidence interval 0.36–0.63), $P<0.0001$) as compared to those transplanted before 1998 using a univariate proportional hazards regression model (Table 3). In the full model adjusting for significant covariates such as age, performance score and donor–recipient match, there was no change in the estimate of the

Table 3 Cox hazard regression model

	P	*RR*	*95% CI*
Univariate model			
Year after 1998	0.0001	0.47	0.36–0.63
Multivariate model			
Year after 1998	0.0001	0.44	0.33–0.59
Age	$P=0.009$		
0–10		1.00	
10–20		1.34	0.88–2.02
20–30		1.43	0.90–2.52
30–40		1.94	1.20–3.14
>40		2.74	1.55–4.85
Interval diagnosis–HSCT	$P=0.91$		
<6 months		1.00	
6–12 months		1.05	0.67–1.66
12–24 months		0.98	0.63–1.54
>24 months		1.11	0.72–1.71
Karnofsky performance status	$P=0.0001$		
Good (80–100)		1.00	
Poor (0–70)		3.80	2.26–6.37
Missing		1.27	0.93–1.73
Donor	$P=0.008$		
Matched unrelated		1.00	
Mismatched unrelated		1.24	1.06–1.54

Abbreviations: RR = relative risk; 95% CI = 95% confidence interval.

Table 2 Univariate outcomes

	Before 1998	*After 1998*	P
N	142	338	
Graft failure (proportion of patients with primary non-engraftment or secondary graft failure) (*n*, (%))	37/142 (26%)	38/338 (11%)	0.0001
Cumulative incidence of acute grade II–IV GvHD (%, 95% CI)	37 (30–45)	28 (23–33)	0.02
Chronic GvHD (proportion of patients alive at 100 days with any grade of cGvHD/patients at risk)	32/85 (38%)	53/245 (22%)	0.006
5-year overall survival (%, 95% CI)	32% (26–40)	57% (49–65)	0.001

Abbreviation: 95% CI = 95% confidence interval.

Table 4 Cause of death

	Before 1998	*After 1998*	P
N patients	149	349	
N deaths (*N*, (% deaths; % all patients))	100	114	0.16*
Graft failure	17 (17%; 11%)	13 (12%; 4%)	
Infection	44 (44%; 30%)	43 (38%; 12%)	
GvHD	8 (8%; 5%)	13 (11%; 4%)	
Transplant related, not specified	6 (6%; 4%)	14 (12%; 3%)	
Secondary malignancy	0 (0%; 0%)	5 (4%; 1%)	
Other	11 (11%; 7%)	13 (11%; 4%)	
Unknown	14 (145; 9%)	13 (11%; 4%)	

**P*-value refers to proportions of causes of death among patients who had died.

year of transplant effect (relative risk: 0.44 (95% confidence interval 0.33–0.59, $P<0.0001$)) (Table 3). As waiting time between diagnosis and transplantation was potentially the most important confounding variable, this variable was forced into the model even though its effect was not significantly associated with outcome. Other covariates such as stem cell source, donor–recipient sex-matching, conditioning regimen and GvHD prophylaxis, were not significantly associated with risk of death. Table 4 shows causes of death. There were no significant differences, but graft failure and infections were less frequently the cause of death in the more recent cohort.

Discussion

This study of a large series of patients receiving unrelated donor transplants for SAA shows that long-term survival has improved considerably since the late 1990s. This improvement is associated with less graft failure and less acute and chronic GvHD, which are important drivers of mortality. The reasons for this improvement are not clear and are not explained by the statistical models presented here. As year of transplantation does not carry any biological relevance, any improvement over time must be due either to changes in patient selection or improved transplant technology. Any variable representing these changes is expected to be more strongly associated with outcome than is year of transplantation, as changes over time are not implemented uniformly across many different countries. We have not found any obvious changes in patient selection. The factors significantly associated with outcomes in studies published previously such as patient age and waiting time between diagnosis and transplantation were, if anything, worse in the more recent cohort. We lacked data on the variables most likely to be associated with these changes, namely, high-resolution HLA typing data and, possibly, treatment of infectious complications by new antifungal and antiviral drugs. The association of improved outcome with improvement in HLA-typing technology is plausible but entirely speculative.

This study has several limitations. It is retrospective, and data were lacking on some aspects of transplant technology such as conditioning regimen and GvHD prophylaxis in a substantial number of patients. These variables did not appear to impact significantly on outcome, whether analyzed in all patients, or in the restricted data set of patients with full information. On some of the outcome variables such as chronic GvHD and graft failure, we lacked time to event information in a large proportion of patients. These outcomes were therefore compared as proportions rather than incidence, and therefore require cautious interpretation. We decided to keep all 498 patients in the analysis as they represent the entire European observational database without any selection, reflecting current practice.

Improvement in the late 1990s is in concordance with technological advances in HLA-typing technology. As compared to matching for six alleles by low or intermediate resolution, many centers nowadays match for 10 alleles by high-resolution technology.[23,24] Another factor may be the increasing size of the donor registries with currently 11 million donors to choose from, a pool that was smaller in the 1990s. The number of unrelated donor transplants per year since 1998 has increased as well, probably reflecting the expectation of better outcome with the availability of better typing technology. During the same time period, there was a much smaller improvement in outcome for recipients of HLA-identical sibling transplants ($n=2052$; 5-year survival 74 ± 3 and $77\pm3\%$; $P=0.03$ for the time periods 1990–1998 and 1998–2005), thus lending support to the hypothesis that most of the improvement in unrelated donor transplantation is due to better donor matching. This is further corroborated by a recently published French study of 89 patients, showing improved survival to be associated with high-resolution HLA matching.[25]

Other studies have reported outcome in patients with SAA transplanted from donors other than HLA-identical siblings using registry data, with survival probabilities of approximately 35%.[11] Some series have reported better results,[19,26–32] for example, in a recent Japanese study of 154 patients showing overall survival of 56%.[26] Donor–recipient HLA disparity was determined using high-resolution techniques, but donor–recipient compatibility was not a significant factor in this study. However, it is likely that mismatches will have an adverse effect on post-transplant survival in less homogenous populations.[10,23,25,29,30] We are not able to address the question of which transplant technology results in best outcomes. We have not found any impact of pretransplant conditioning or GvHD prophylaxis, but our ability to detect differences is limited due to missing data. Some smaller series have reported interesting results using low-dose TBI[29] or fludarabine,[31] but this requires validation in larger studies.

We found a highly significant improvement in survival in patients transplanted after 1998 as compared to earlier transplants. There is no evidence for differences in patient selection. The most likely explanation for this improvement is progress in donor selection through high-resolution HLA typing technology, and possibly, improved infection control. The currently used algorithms of when to initiate an unrelated donor search in SAA patients need to be revised in the light of these data.

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