Impact of age on outcomes after bone marrow transplantation for acquired aplastic anemia using HLA-matched sibling donors

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ABSTRACT

Background
Transplantation from an HLA-matched sibling is the treatment of choice for young patients with acquired severe aplastic anemia. For older patients, the acceptable upper age limit for transplantation as first-line treatment varies. The current analysis, therefore, sought to identify age or ages at transplantation at which survival differed.

Design and Methods
We studied the effect of patients' age, adjusting for other significant factors affecting outcomes, in 1307 patients with severe aplastic anemia after HLA-matched sibling transplantation using logistic and Cox regression analysis. Age categories (<20 years, 20-40 years, >40 years) were determined using Martingale residual plots for overall survival and categories based on differences in survival.

Results
Patients aged over 40 years old were more likely to have had immunosuppressive therapy, a poor performance score and a longer interval between diagnosis and transplantation. Neutrophil recovery was similar in all age groups but patients aged over 40 years had a lower likelihood of platelet recovery compared to patients aged less than 20 years (OR 0.45, P=0.01) but not compared to those aged 20-40 years (OR 0.60, P=0.10). Compared to the risk of mortality in patients aged less than 20 years, mortality risks were higher in patients over 40 years old (RR 2.70, P<0.0001) and in those aged 20-40 years (RR 1.69, P<0.0001). The mortality risk was also higher in patients aged over 40 years than in those 20-40 years old (RR 1.60, P=0.008).

Conclusions
Mortality risks increased with age. Risks were also higher in patients with a poor performance score and when the interval between diagnosis and transplantation was longer than 3 months, implying earlier referral would be appropriate when this treatment option is being considered.

Key words: severe aplastic anemia, transplantation, patient age, HLA-identical sibling donor, overall survival.

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Introduction

Bone marrow transplantation from an HLA-matched sibling is the treatment of choice for young patients with severe acquired aplastic anemia.[1-4] In the absence of such a donor, immunosuppressive therapy with anti-thymocyte globulin and cyclosporine may be equally successful.[1,2] The upper age limit for an HLA-matched sibling transplant as first-line therapy for severe aplastic anemia varies with transplant center. While some support this treatment as first-line therapy for patients up to the age of 50-55 years,[3,5,6] others limit transplantation as first-line treatment to those younger than 40 years.[1,4,7-9] At these centers, patients aged over 40 years receive immunosuppressive therapy as first-line treatment and transplantation from a matched sibling is reserved to those in whom the immunosuppressive therapy fails. There is general agreement that the risks of morbidity and mortality from the transplantation procedure increase with age and consequently so to does the desire to avoid this procedure in older persons.

The effect of age on transplant outcomes in severe aplastic anemia is, however, unclear, with some reports suggesting an adverse impact[3,8-12] and others suggesting an outcome comparable to that observed in younger patients.[13,14] The best first-line treatment option for older patients with severe aplastic anemia is, therefore, debatable and this has led to the practice of offering immunosuppressive therapy as first-line treatment to older patients despite the availability of a matched sibling.[1] Transplantation is offered after failure of one to two courses of immunosuppressive therapy. About 60-75% of patients do respond to immunosuppressive therapy with the response taking approximately 3-6 months.[2] As with transplantation, survival after immunosuppressive therapy is associated with age. Older patients who respond to immunosuppressive therapy have a 5-year survival rate of about 50% which is considerably lower than the 90% seen in younger patients.[5] For the non-responder with a matched sibling, immunosuppressive therapy delays transplantation and exposes the patient to risks of transfusions, including allosensitization and iron overload, prolonged neutropenia and infections and possibly poor performance scores.

The dilemma of whether to offer a matched sibling transplant to an older patient who is at higher risk of graft-*versus*-host disease (GVHD) and consequently higher morbidity and mortality must be weighed carefully against the benefits of immunosuppressive therapy which may produce a sustained remission but is associated with late clonal abnormalities, myelodysplastic syndrome and acute myeloid leukemia. The current analysis, therefore, had two objectives: (i) to identify the age or ages at transplantation beyond which transplant outcomes differ, and (ii) to identify risk factors that may be modified to improve survival after HLA-matched sibling donor transplantation for patients, including older ones, with severe aplastic anemia.

Design and Methods

Data source

The characteristics of the patients, their disease and transplants and outcome data were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is a voluntary working group of over 400 transplant centers worldwide that contribute data on consecutive transplants to a Statistical Center at the Medical College of Wisconsin. Compliance and data quality are monitored by on-site audits and all patients are followed longitudinally, annually. This study was approved by the Institutional Review Board of the Medical College of Wisconsin.

Inclusion criteria

Patients with acquired severe aplastic anemia who received their first HLA-matched sibling donor bone marrow transplant between 1991 and 2004 and received calcinuerin inhibitor-containing GVHD prophylaxis could be included in this study. Recipients of HLA-matched sibling transplants with peripheral blood progenitor cells, those who did not receive calcinuerin inhibitor-containing GVHD prophylaxis, patients with Fanconi anemia and those with congenital bone marrow failure were excluded.

Outcomes

Neutrophil recovery was defined as achieving an absolute neutrophil count of 0.5×10^9/L or greater for 3 consecutive days and an unsupported platelet count of 20×10^9/L or greater for 7 days. Acute and chronic GVHD were diagnosed and graded according to defined criteria.[15,16] Secondary graft failure was evaluated in patients who had achieved neutrophil recovery and experienced a subsequent decline in neutrophil count to below 0.5×10^9/L without recovery. Death from any cause was considered an event and surviving patients were censored at last follow-up.

Statistical analysis

The probabilities of hematopoietic recovery and acute and chronic GVHD were calculated using the cumulative incidence function estimator with death as the competing risk.[17] The probability of overall survival was calculated using the Kaplan-Meier estimator.[18] The 95% confidence interval (CI) was estimated using log transformation. Logistic regression models for neutrophil and platelet recovery and Cox proportional hazards models for GVHD and overall mortality were used to evaluate potential prognostic factors for the outcomes of interest. All models were constructed using a backward selection, with a P value of 0.01 or less indicating statistical significance (Bonferroni's correction). The main effect tested in all multivariate analyses for the outcomes of interest was age: less than 20 years *versus* 20-40 years old *versus* over 40 years of age. The age categories were determined with Martingale residual plots for overall survival and categories based on differences in overall survival. Other variables considered were: pre-transplantation performance score (<90% *versus* ≥90%), number of blood transfusions pre-transplant (<20 *versus* 20-50 *versus* >50), immunosuppressive therapy prior to transplant (yes *versus* no), transplant conditioning regimen (cyclophosphamide plus antithymocyte globulin or limited field irradiation *versus* cyclophosphamide alone *versus* busulfan plus cyclophosphamide or fludarabine plus other agents), time from diagnosis to transplant (≤3 months *versus* >3 months), donor-recipient gender match (female donors to male recipients *versus* female donors to female recipients *versus* male donors to female recipients *versus* male donors to male recipients), donor-recipient cytomegalovirus serostatus (donor and recipient positive *versus* donor positive, recipient negative *versus* donor negative, recipient positive *versus* donor and recipient negative), ABO incompatibility (none *versus* minor *versus* major) and year of transplant (1991-1994 *versus* 1995-1998 *versus* 1999-2002 *versus* 2003-2004). Time-dependent covariates were used to assess the proportionality assumption and there were no violations. All P

values are two-sided and analyses were done using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

Results

The characteristics of the patients, their disease and transplants are shown in Table 1. Overall 1,307 patients received bone marrow grafts from their HLA-matched sibling. Cyclophosphamide alone or with anti-thymocyte globulin was the predominant transplant preparatory regimen. All patients received calcinuerin inhibitor-containing GVHD prophylaxis. The characteristics of patients in the three age groups were similar except patients aged over 40 years old were more likely to have had a poor performance score (38% *versus* 46% *versus* 54%; *P*=0.002), have received immunosuppressive therapy prior to transplantation (46% *versus* 50% *versus* 65%; *P*=0.001), and to have had an interval longer than 3 months between diagnosis and transplantation (37% *versus* 45% *versus* 50%; *P*=0.003). Of the 84 patients in the oldest age group, 54 (64%) were aged 41-50 years and only 6 patients were older than 60 years. The transplants were conducted in 200 centers worldwide. The median follow-up of surviving patients is 7 years.

Hematopoietic recovery

Neutrophil recovery rates were similar in the three age groups (Table 2A) after adjusting for transplant condition-

Table 1. Characteristics of the patients, disease and transplants.

Variable	Age at transplantation <20 years Number (%)	20-40 years Number (%)	>40 years Number (%)	*P* value
Number of patients	717	506	84	
Male	430 (60)	320 (63)	49 (58)	0.443
Performance score				0.002
<90	273 (38)	234 (46)	45 (54)	
90	431 (60)	270 (53)	37 (44)	
Not reported	13 (2)	2 (<1)	2 (2)	
Blood transfusions prior to transplantation				0.042
<20	301 (42)	188 (37)	30 (36)	
20-50	177 (25)	110 (22)	18 (21)	
>50	102 (14)	102 (20)	17 (20)	
Not reported	137 (19)	106 (21)	19 (23)	
Conditioning regimen				0.003
Cyclophosphamide + anti-thymocyte globulin	354 (49)	194 (38)	40 (48)	
Cyclophosphamide alone	187 (26)	137 (27)	22 (26)	
Cyclophosphamide + limited field irradiation	55 (8)	52 (10)	11 (13)	
Busulfan +cyclophosphamide	105 (15)	110 (22)	9 (11)	
Fludarabine + other agents*	16 (2)	13 (3)	2 (2)	
Time from diagnosis to transplant, months				0.003
≤3	453 (63)	277 (55)	42 (50)	
>3	264 (37)	229 (45)	42 (50)	
Immunosuppresive therapy prior to transplant	329 (46)	247 (49)	50 (60)	0.057
Donor - recipient sex match				0.850
Male donor – male recipient	240 (33)	180 (36)	28 (33)	
Male donor – female recipient	165 (23)	107 (21)	23 (27)	
Female donor – male recipient	189 (26)	140 (28)	21 (25)	
Female donor – female recipient	122 (17)	79 (16)	12 (14)	
Not reported	1 (<1)	---	---	
Donor - recipient cytomegalovirus serostatus				0.015
Donor positive – recipient positive	363 (51)	285 (56)	42 (50)	
Donor positive – recipient negative	42 (6)	26 (5)	9 (11)	
Donor negative – recipient positive	106 (15)	76 (15)	13 (15)	
Donor negative – recipient negative	162 (23)	77 (15)	11 (13)	
Not reported	44 (6)	42 (8)	9 (11)	
GVHD prophylaxis				0.623
Cyclosporine +methotrexate ± other	617 (86)	432 (85)	69 (82)	
Cyclosporine ± other	100 (14)	74 (15)	15 (18)	
Year of transplant				0.129
1991-1994	530 (74)	393 (78)	61 (73)	
1995-1998	115 (16)	69 (14)	19 (23)	
1999-2002	72 (10)	44 (9)	4 (5)	
2003-2004	530 (74)	393 (78)	61 (73)	
Median follow-up of survivors, months	82 (3 - 197)	97 (3 - 193)	83 (1 - 171)	

**Other agents used with fludarabine: fludarabine + busulfan ± anti-thymocyte globulin (n=17), fludarabine + cyclophosphamide (n=11), fludarabine + melphalan ± anti-thymocyte globulin (n=1), fludarabine + total body irradtiation (n=1) and fludarabine + anti-thymocyte globulin (n=1).*

ing regimen, the only risk factor associated with neutrophil recovery. The cumulative incidences of neutrophil recovery at day 28 in patients aged less than 20 years, 20-40 years and greater than 40 years were 83% (95% CI 80-86), 87% (95% CI 83-90) and 88% (95% CI 79-94), respectively. Recovery rates were lower in patients conditioned with cyclophosphamide alone (OR 0.42, 95% CI 0.29-0.59; *P*<0.0001) or busulfan plus cyclophosphamide or fludarabine-containing regimens (OR 0.48, 95% CI 0.32-0.72; *P*=0.0003) than in patients conditioned with cyclophosphamide plus anti-thymocyte globulin or limited field irradiation.

Unlike neutrophil recovery, platelet recovery differed with age at transplantation (Table 2A). Recovery rates were lower in patients aged over 40 years old. The cumulative incidences of platelet recovery on day 100 in patients aged less than 20 years, 20-40 years and over 40 years old were 90% (95% CI 87-92), 86% (95% CI 83-89) and 79% (95% CI 68-86), respectively. Additionally, the platelet recovery rate was lower in patients with a poor performance score, independently of age (OR 0.44, 95% CI 0.31-0.63; *P*<0.0001). The transplant conditioning regimen was not associated with platelet recovery. We also looked for an effect of prior immunosuppressive therapy on hematopoietic recovery. The odds ratio for neutrophil recovery in patients who received immunosuppressive therapy prior to transplantation compared to those who did not receive immunosuppressive therapy was 1.45 (95% CI 1.06-1.98; *P*=0.02) whereas the corresponding odds ratio for platelet recovery was 0.77 (95% CI 0.55-1.10; *P*=0.15).

Among patients (n=1208) who achieved neutrophil recovery, 125 had secondary graft failure. Most failures occurred within 2 years from transplantation. In multivariate analysis, there were no significant differences in secondary graft failure rates among the three age groups (Table 2A). However, the secondary graft failure rate was higher when cyclophosphamide alone was the transplant conditioning regimen (OR 2.02, 95% CI 1.33-3.06; *P*=0.001) or busulfan plus cyclophosphamide or fludarabine-containing regimens were used (OR 2.30, 95% CI 1.44-3.66; *P*=0.001) compared to when the conditioning regimen was cyclophosphamide plus anti-thymocyte globulin or with limited field irradiation.

Table 2A. Results of multivariate analysis for hematopoietic recovery and secondary graft failure.

Variables	Odds Ratio (95% Confidence Interval)	*P* value
Neutrophil recovery at day 28*		
Age at transplant		
20-40 *vs.* <20 years	1.44 (1.03-2.00)	0.030
>40 *vs.* <20 years	1.52 (0.76-3.05)	0.237
>40 *vs.* 20-40 years	1.06 (0.52-2.17)	0.877
Platelet recovery at day 100†		
Age at transplant		
20-40 *vs.* <20 years	0.75 (0.52-1.09)	0.133
>40 *vs.* <20 years	0.45 (0.25-0.83)	0.010
>40 *vs.* 20-40 years	0.60 (0.33-1.10)	0.098
Secondary graft failure at 2 years‡		
Age at transplant		
20-40 *vs.* <20 years	0.75 (0.51-1.12)	0.167
>40 *vs.* <20 years	1.69 (0.87-3.29)	0.120
>40 *vs.* 20-40 years	2.24 (1.11-4.53)	0.025

**Model also adjusted for conditioning regimen; †Model also adjusted for performance score ‡Model also adjusted for conditioning regimen.*

Table 2B. Results of multivariate analysis for GVHD and overall mortality.

Variables	Relative Risk (95% Confidence Interval)	*P* value
Acute GVHD grade 2-4		
Age at transplant		
20-40 *vs.* <20 years	1.64 (1.21 - 2.22)	0.001
>40 *vs.* <20 years	2.87 (1.79 - 4.60)	<0.0001
>40 *vs.* 20-40 years	1.75 (1.10 - 2.80)	0.019
Chronic GVHD†		
Age at transplant		
20-40 *vs.* <20 years	2.55 (1.91 - 3.41)	<0.0001
>40 *vs.* <20 years	3.59 (2.23 - 5.78)	<0.0001
>40 *vs.* 20-40 years	1.41 (0.89 - 2.22)	0.143
Overall mortality‡		
Age at transplant		
20-40 *vs.* <20 years	1.69 (1.33 - 2.14)	<0.0001
>40 *vs.* <20 years	2.70 (1.89 - 3.87)	<0.0001
>40 *vs.* 20-40 years	1.60 (1.13 - 2.26)	0.008

†Model also adjusted for performance score ‡Model also adjusted for interval from diagnosis to transplant and transplant conditioning regimen.

Acute and chronic graft-versus-host disease

Compared to the risks of grade 2-4 acute GVHD and chronic GVHD in patients aged less than 20 years, the risks were higher in patients aged 20-40 years old and in those over 40 years old (Figure 1A, B, Table 2B). The risk of acute but not chronic GVHD was higher in patients aged more than 40 years compared to the risk in patients aged 20-40 years. Among the patients with chronic CVHD, 51% had limited disease and 49% had extensive disease. The proportions of patients with limited and extensive chronic GVHD were similar across the three age groups. The risk of chronic GVHD was higher in patients with poor performance scores (RR 1.59, 95% CI 1.20-2.04; *P*=0.001).

Overall survival

Mortality risks after transplantation increased with age. Compared to the risk in patients aged less than 20 years, mortality risks were higher in those aged 20-40 years and in those over 40 years old (Table 2B). The risk of mortality was also higher in patients aged over 40 years than in those aged 20-40 years. Independently of the age at transplantation, mortality risks were higher in patients with a poor performance score (RR 1.79, 95% CI 1.42-2.22; *P*<0.0001), in those who had waited longer than 3 months from diagnosis to transplantation (RR 1.58, 95% CI 1.26-1.99; *P*<0.0001), and in patients whose transplant conditioning regimen was busulfan plus cyclophosphamide or contained fludarabine (RR 1.79, 95% CI 1.36-2.36; *P*<0.0001). The 5-year probabilities of overall survival adjusted for performance score, waiting time to transplantation, and transplant conditioning regimen were 82% (95% CI 80-85), 72% (69-74) and 53% (47-58) in patients aged under 20 years old, 20-40 years and over 40 years old, respectively (Figure 2). In all age groups, mortality was higher after the development of chronic GVHD (RR 1.49, 95% CI 1.07-2.09; *P*=0.019). Similarly, mortality was also higher after development of acute GVHD in all age groups (RR 3.63, 95% CI 2.82-4.67; *P*<0.0001).

We examined whether immunosuppressive therapy prior to transplantation had an effect, adjusting for age at

transplantation, and found none (RR 0.96, 95% CI 0.75-1.23; *P*=0.75). We also looked for an effect of immunosuppressive therapy prior to transplantation considering waiting time to transplant. A longer waiting period (>3 months) from diagnosis to transplantation was associated with higher mortality, independently of immunosuppressive therapy. Mortality risks were higher in patients who waited longer than 3 months from diagnosis to transplantation if they had received immunosuppressive therapy (RR 1.44, 95% CI 1.03-2.01; *P*=0.031) or had not received this treatment (RR 1.83, 95% CI 1.29-2.60; *P*=0.001) implying delays in excess of 3 month increase the risk of death independently of treatment prior to transplantation.

Causes of death within and beyond 100 days are shown in Tables 3A and 3B. Infection and other transplant-related complications accounted for most deaths; there were no significant differences in causes of death among the three age groups.

Table 3A. Causes of early mortality (within 100 days after transplantation).

	Age at transplantation			
	<20 years (%)	20-40 years (%)	>40 years (%)	
	Number	Number	Number	*P* value
Number of patients	60	69	22	0.199
Graft failure*	15 (25)	9 (13)	3 (14)	
Infection	23 (38)	16 (23)	6 (27)	
Interstitial pneumonia	2 (3)	4 (6)	3 (14)	
Acute respiratory distress syndrome	1 (2)	6 (9)	1 (5)	
GVHD	5 (8)	9 (13)	2 (9)	
Organ failure	7 (12)	8 (12)	2 (9)	
Hemorrhage	6 (10)	16 (23)	4 (18)	
Other**	1 (2)	0	1 (5)	
Unknown	0	1 (1)	0	

**Two patients had secondary graft failure; **Others were microangiopathic thombotic thrombocytopenia (n=1) and cerebral toxoplasmosis (n=1).*

Table 3B. Causes of late mortality (beyond 100 days after transplantation).

	Age at transplantation			
	<20 years (%)	20-40 years (%)	>40 years (%)	
Causes of death	Number	Number	Number	*P* value
Number of patients	63	89	22	0.944
Primary disease	3 (5)	4 (4)	1 (5)	
Graft failure*	9 (14)	13 (15)	2 (9)	
Infection	11 (17)	22 (25)	3 (14)	
Interstitial pneumonia	3 (5)	1 (1)	1 (5)	
Acute respiratory distress syndrome	1 (2)	4 (4)	1 (5)	
GVHD	10 (16)	11 (12)	4 (18)	
Organ failure	9 (14)	12 (13)	1 (5)	
New malignancy	1 (2)	2 (2)	1 (5)	
Hemorrhage	7 (11)	5 (6)	2 (9)	
Other**	3 (5)	4 (4)	1 (5)	
Unknown	6 (10)	11 (12)	5 (23)	

**Thirteen patients had secondary graft failure; **Others were accidental death including suicides (n=6), thromboembolism (n=1), pulmonary complication, undetermined etiology (n=1).*

Discussion

The current analysis had two objectives: (i) to identify an optimal upper age limit above which survival differs and (ii) to identify risk factors associated with survival after HLA-matched sibling donor transplant for severe aplastic anemia. We identified three age cut-offs with survival differences: younger than 20 years, 20-40 years and older than 40 years. There was a 10-20% absolute difference in overall survival between these age groups, after adjustment for other factors found to be associated with an adverse survival outcome: poor performance score,

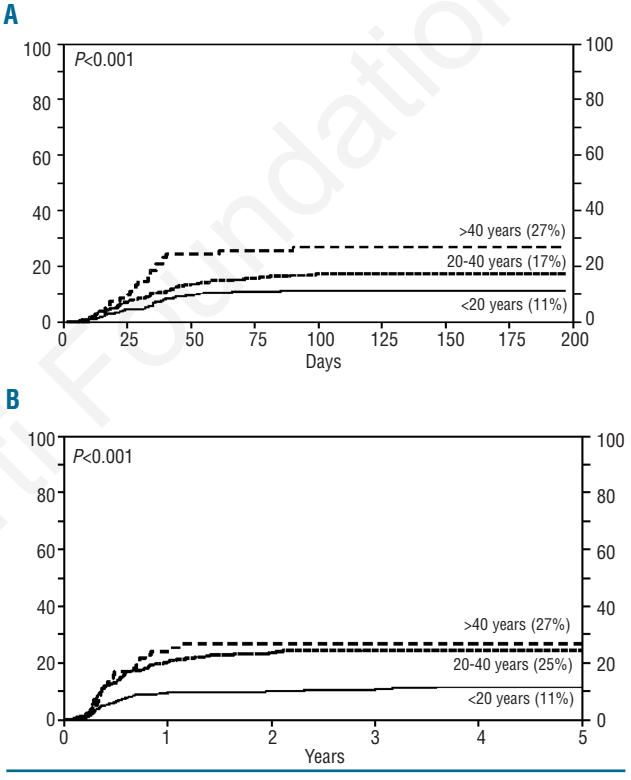

Figure 1. (A) Cumulative incidence of acute GVHD. (B) Cumulative incidence of chronic GVHD.

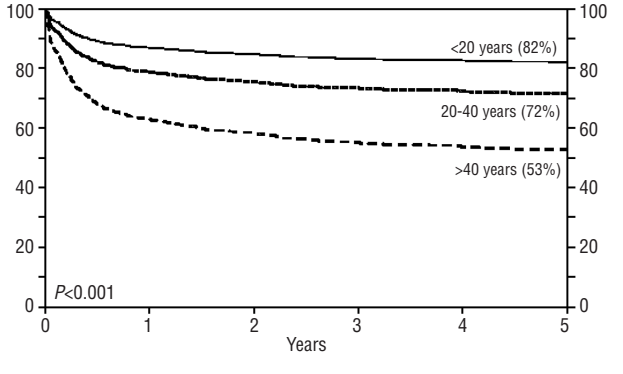

Figure 2. Probability of overall survival adjusted for performance score, waiting time to transplantation and transplant conditioning regimen.

longer interval from diagnosis to transplantation (>3 months) and transplant conditioning regimen. The best results were seen in patients younger than 20 years at transplantation and those aged 20-40 years fared better than those older than 40 years. Our observations confirm and extend those of others.[1,10]

The current analysis supports the practice of transplantation within 3 months of diagnosis, resulting in higher survival rates compared to transplantation occurring more than 3 months after diagnosis, regardless of the patients' age or immunosuppressive therapy prior to transplantation. The delay between diagnosis and transplantation is a modifiable factor and if transplantation is being considered, our data support early referral. Our observations do, however, differ from those reported by Ades *et al.* who found that both a long interval between diagnosis and transplantation and treatment with immunosuppressive therapy or androgens prior to transplantation had adverse effects on survival.[10] Unlike the data analyzed by Ades *et al.*, the data herein were reported by 200 transplant centers and about half the transplants were performed in South or Central America, the Middle East, Asia or Africa. In these regions immunosuppressive therapy was used as first-line therapy in approximately 50% of patients including those aged under 20 years and a third of the patients who received their transplant within 3 months from diagnosis also received immunosuppressive therapy. All of these factors may explain our inability to detect meaningful differences in survival between those who received immunosuppressive therapy and those who proceeded to transplantation as first-line therapy. Nevertheless, delaying transplantation beyond 3 months after diagnosis had an adverse effect on survival and efforts to limit delays must be encouraged.

The data indicate that patients over 40 years old were more likely to receive immunosuppressive therapy. For these patients, the observed 5-year overall survival rate after immunosuppressive therapy (in responders) and transplantation was similar.[19] As approximately 60-75% respond to immunosuppressive therapy and 35-45% of responders experience disease recurrence, when deciding the first-line therapy for severe aplastic anemia (transplantation of bone marrow from a matched sibling or immunosuppressive therapy), the risks and benefits of each treatment option as well as the severity of the aplastic anemia must be considered. In an early study, older patients with less severe disease fared poorly after transplantation.[8] Though the survival rate after hematopoietic cell transplantation was higher when transplantation occurred within 3 months from diagnosis, GVHD risks were higher in patients over 40 years old and the adverse effect of acute and chronic GVHD on survival is a limitation. This compels us to re-evaluate current GVHD prophylaxis strategies in an attempt to lower the risk of GVHD and its deleterious effect on survival. The risk of developing a malignancy is also high in survivors of severe aplastic anemia after immunosuppressive therapy or transplantation. Myelodysplastic syndrome and acute myeloid leukemia tend to occur more commonly after immunosuppressive therapy than after transplantation, whereas solid tumors occur at the same rate after transplantation and immunosuppressive therapy.[5,10,19-21] In the absence of a direct comparison of treatment outcomes of older patients who received immunosuppressive therapy and transplantation as first-line therapy, the optimal treatment strategy for the older patient cannot be determined.

Transplant conditioning regimens were associated with survival, neutrophil recovery and secondary graft failure. Cyclophosphamide plus anti-thymocyte globulin or limited field irradiation appears to be the optimal regimen. The observed disadvantage with busulfan plus cyclophosphamide and fludarabine-containing regimens contrasts with reports of successes with busulfan and fludarabine-containing regimens.[12,22-25] Most of these reports included relatively few patients and none compared the various regimens directly. More definitive studies are, therefore, needed before widespread adoption of conditioning regimens other than cyclophosphamide plus anti-thymocyte globulin.

As with any study based on registry data, our analysis has several limitations. Information was not collected on the number of cycles of immunosuppressive therapy, the drugs that were used or why several patients aged less than 20 years received immunosuppressive therapy. Treatment choices including the decision to offer transplantation and its timing, conditioning regimen and GVHD prophylaxis are at the discretion of the treating physician. Taking into consideration the study by Socié *et al.*[26] on late mortality, in which the risk of late deaths for patients with severe aplastic anemia after HLA-matched sibling transplantation was similar to that of the general population 6 years after transplantation, the data support early referral if HLA-matched sibling transplantation is being considered. The question of immunosuppressive therapy *versus* transplantation as first-line therapy for the older patient should ideally be examined in a controlled, randomized trial. Given that no such trial is on-going or planned and that there is an absence of data in the current era supporting one treatment option over another, the decision on which first-line treatment to use for older patients with aplastic anemia and a matched sibling remains the choice of the treating physician and the patient.

Authorship and Disclosures

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