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Bone marrow transplantation for severe aplastic anemia: the Barcelona Hospital Clinic experience

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Abstract

Background and Objective. The outcome of patients with severe aplastic anemia (SAA) has improved considerably over the last decades. Bone marrow transplantation (BMT) is the treatment of choice in young patients who have an HLA-identical sibling donor. This study analyzes the outcome and factors related to survival in patients with SAA receiving BMT in our Institution.

Design and Methods. Between March 1978 and December 1996, 49 consecutive patients received an HLA-identical sibling marrow transplant for SAA. Median age was 21 years (range, 4 to 47) and 15 (31%) were women. Median interval from diagnosis to transplant was 2.6 months (range, 0.5 to 159). Between 1978 and 1982 all patients were conditioned with cyclophosphamide (CY) alone and received methotrexate (MTX) until day 102 as graft-versus-host disease (GvHD) prophylaxis. From 1983 most patients received CY and thoraco-abdominal irradiation (TAI) as the conditioning regimen and cyclosporin A (CSA) as GvHD prophylaxis.

Results. Survival probability at 10 years was 55±7% with a median follow-up for the surviving patients of 8.5 years. The incidences of graft failure, grade II to IV acute GvHD, and chronic GvHD were 21%, 39.5% and 31%, respectively. In multivariate analysis three factors adversely influenced survival: a) age ≥ 30 years (p = 0.05); b) ≥ 10 transfusion units pre-BMT (p = 0.008); and c) use of long course MTX for GvHD prophylaxis (p = 0.01). One case of squamous-cell carcinoma occurred in a TAI-treated patient 13 years post-transplantation.

Interpretation and Conclusions. BMT is effective in young patients with SAA who have an HLA-identical sibling donor, particularly if minimally transfused pre-transplant. The introduction of TAI and CSA to our preparative regimen has led to a remarkably increased survival.

Key words: bone marrow transplantation, severe aplastic anemia, treatment

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The outcome of patients with acquired severe aplastic anemia (SAA) has improved considerably over the last decades.[1] Today, immunosuppression (IS) and bone marrow transplantation (BMT) are the best established therapeutic options.[2,3] The choice between them should take into account not only the immediate results but also the late complications of each treatment modality. High response rates and long-term survival have been achieved with IS but some patients require transfusional support or may develop late clonal abnormalities.[4-8]

BMT is the elective treatment in young patients who have an HLA-identical sibling donor. Recent studies report 60-70% long-term survival but a proportion of patients have chronic graft-versus-host disease (GvHD), chronic organ impairment due to the conditioning regimen or secondary malignancies years after the end of the treatment.[9-13] Several factors identified in large multicenter studies have been correlated with the outcome of patients treated with BMT: patient's age,[10] sex-match between donor and recipient,[12] interval from diagnosis to transplant,[12] number of previous transfusions,[14] refractoriness to random donor platelets,[14] marrow cell dose,[15] type of prophylaxis of GvHD,[16] graft failure,[17] and incidence and severity of acute GvHD.[14]

The aim of the present study was to analyze the outcome and factors related to survival in 49 consecutive patients with acquired SAA receiving BMT from an HLA-identical sibling in our Institution during the last 20 years.

Design and Methods

Between March 1978 and December 1996, 49 consecutive patients received an HLA-identical sibling marrow transplant for acquired SAA in our Institution. All patients fulfilled the diagnostic criteria for SAA described by Camitta *et al*.[18] The characteristics of the patients, disease and previous treatments are summarized in Table 1. Median age was 21 years (range, 4 to 47); 15 patients (31%) were women and 34 were men. Nineteen (39%) patients had a very

Table 1. Patients, disease and previous treatments.

Characteristics	Value	
No. patients	49	
Year of transplant		
1978-83	26	
1984-96	23	
Patient age (years)*	21	(4-47)
Disease severity		
Severe	30	61%
Very severe°	19	39%
Interval diagnosis-BMT (months)*	2.6	(0.6-159.6)
Etiology		
Idiopathic	43	88%
Chemical	3	6%
Posthepatitis	3	6%
Previous treatment of aplasia		
None	19	39%
Androgens ± corticosteroids	19	39%
Immunosuppressive therapy	11	22%
No. previous transfusions (units)*	22	(3-300)
< 10 units	10	20%

**Median (range); °granulocytes count below 0.2×10⁹/L.*

severe aplastic anemia as defined by a neutrophil count < 0.2×10⁹/L.[3] In 43 cases (88%) the etiology of the aplasia was unknown. The median interval between diagnosis of SAA and transplant was 2.6 months, ranging from two weeks to more than 13 years. Nineteen patients (39%) did not receive any treatment before BMT, 19 had been treated with androgens with or without corticosteroids and the remaining eleven (22%) with immunosuppressive therapy (cyclosporin A one case, ATG one case, or both nine cases). All patients had received transfusions before transplantation, the median number of transfused units being 22 (range, 3 to 300). The main BMT characteristics are summarized in Table 2. Twelve patients were ABO mismatched with the donor. In eight cases a high-volume plasma-exchange was performed and in four the graft was depleted of erythrocytes by centrifugation or dextran sedimentation. Before transplantation, seven patients (14%) were refractory to random donor platelets. Six patients (12%) had serum transaminase levels more than double normal values. Twenty-three patients (47%) showed clinical signs of infection in the week before transplantation. Finally, the median Karnofsky score of the whole series was 30% (range, 20 to 90%). Between 1978 and 1982 all patients received cyclophosphamide (CY) 200 mg/kg alone as conditioning regimen and a long course of methotrexate (MTX) until day 102 as GvHD prophylaxis. From 1983 most patients were treated with CY plus thoraco-abdominal irradiation (TAI) (6 Gy single dose) and cyclosporin A (CSA) (12 mg/kg/day). One patient had a preparative regimen consisting of CY and ATG 90 mg/kg and was evaluated together with non-irradiated patients. All patients were treated in high-efficiency particulate air-filtered or laminar airflow rooms and received oral non-absorbable antibiotics and low microbial diet for gut decontamination. Trimethoprim-sulfamethoxazole or inhaled pentamidine were administered for *Pneumocystis carinii* prophylaxis. From January 1989 all patients received prophylactic intravenous immunoglobulin. All transfused blood products were irradiated (20 Gy) before infusion. All patients received psychological support during and after the transplant procedure and were followed by ophthalmologists, endocrinologists and chest specialists for early detection of possible side-effects.[19,20]

Statistical analysis

Results were analyzed as of January 1997. Graft failure was analyzed in patients surviving ≥ 21 days from marrow infusion and was defined as either primary graft failure (no engraftment) or transient engraftment (recovery of donor hematopoiesis followed by loss of the graft) using published criteria.[21] Patients surviving ≥ 21 days and ≥ 100 days, with engraftment, were considered at risk of acute and chronic GvHD, respectively. Assessment and grading of acute and chronic GvHD were performed as previously described.[22,23] Treatment of acute GvHD var-

Table 2. BMT characteristics.

Characteristics	Value	
Donor age (years)*	21	(2-40)
Sex of donor-patient		
Male-male	16	33%
Male-female	6	12%
Female-female	9	18%
Female-male	18	37%
ABO mismatch	12	25%
Recipient plasma-exchange	8	
Marrow erythrocyte depletion	4	
Refractoriness to random donor platelets	7	14%
Liver impairment pretransplantation	6	12%
Infection in week before transplantation	23	47%
Karnofsky score pre-BMT (%)*	30	(20-90)
Preparative regimen		
CY only	21	43%
CY+ATG	1	2%
CY+TAI	27	55%
GvHD prophylaxis		
CSA only	24	49%
MTX only	25	51%
Marrow nucleated cell dose (×10⁸/kg)*	2.6	(0.4-5.6)

**Median (range). Cy: cyclophosphamide; ATG: anti-thymocyte globulin; TAI: thoracoabdominal irradiation; CSA: cyclosporin A; MTX: methotrexate.*

ied with time and included corticosteroids, ATG, and CSA. Therapy for chronic GvHD also varied and included corticosteroids, azathioprine, CSA, and thalidomide, alone or in combination.[19]

Univariate analyses were used to test associations between patient-, donor-, disease- and transplant-related variables and the probability of survival, acute GvHD and graft failure. Curves were calculated with the method of Kaplan and Meier and then compared by the log-rank test.[24,25] Survival data were censored as of the date of last contact or second treatment after graft failure (second BMT, ATG, or other). Pre-transplant risk factors for survival were examined in multivariate analysis using a Cox proportional hazards regression model. For all these studies, the BMDP statistical package was employed.

Results

Engraftment

Six of the 49 (12%) patients died within the first 21 days after BMT and were not evaluable for engraftment. Causes of death were infection (n = 3), hemorrhage (n = 1), liver veno-occlusive disease (VOD) (n = 1) and cardiac toxicity following conditioning (n = 1). Median time to recovery of granulocytes to $\geq 0.5 \times 10^9$/L was 17 days (range, 11 to 33) and differed according to the type of prophylaxis for GVHD; in patients who received long-term MTX the median time was 21.5 vs 14 days in those treated with CSA (p = 0.01). Graft failure occurred in nine of the 43 (21%) patients at risk with an actuarial probability of 25±7% at five years. The type of conditioning regimen and/or GvHD prophylaxis had a major impact on the probability of graft failure. None of the 24 patients treated with TAI and CSA rejected the graft; in contrast, nine of the 25 (36%) patients receiving CY alone and MTX had graft rejection (p < 0.001). One patient had primary graft failure and eight had transient engraftment with loss of the graft between one and 36 months (median, 2.5) after transplant. Four of the nine (44%) patients who failed to engraft died due to infection (n = 3) or hemorrhage (n = 1) at a median of 1.5 months post-transplantation (range, 1 to 2.5). Three patients received a second BMT from the same donor three, four, and nine months after the first transplant, respectively. Only one of these three patients is alive eight years after BMT while the other two died due to severe acute GvHD and second graft failure at 2.5 and five months. The remaining two patients had an autologous recovery 2.5 and 36 months post-transplantation.

Graft-versus-host disease

Seventeen of the 43 (39.5%) patients at risk developed grade II to IV acute GvHD and the actuarial probability at four months was 43±8%. In six of these 17 (35%) patients this complication was the primary cause of death. In univariate analysis the only factor associated with a higher risk of acute GvHD was the type of conditioning regimen. Patients treated with TAI had a probability of grade II to IV acute GvHD of 56% vs 27% in those given CY alone (p = 0.02). Nine of 29 (31%) patients at risk developed a chronic extensive GvHD (in five cases evolving from a grade II-IV acute GvHD), and the actuarial probability at two years was 31 ± 9%. Chronic extensive GvHD was an important contributory cause of death in two of the nine (22%) patients.

Survival

Survival probability of the whole series at 10 years was 55±7% with a median follow-up for the surviving patients of 8.5 years (range, 0.1 to 15.7). Survival rate was 39±10% for patients transplanted before 1984 and 73±9% for those who had transplantation after 1984 (p = 0.04)(Figure 1). Twenty-one of 49 (43%) patients died between day 0 and 14.5 months

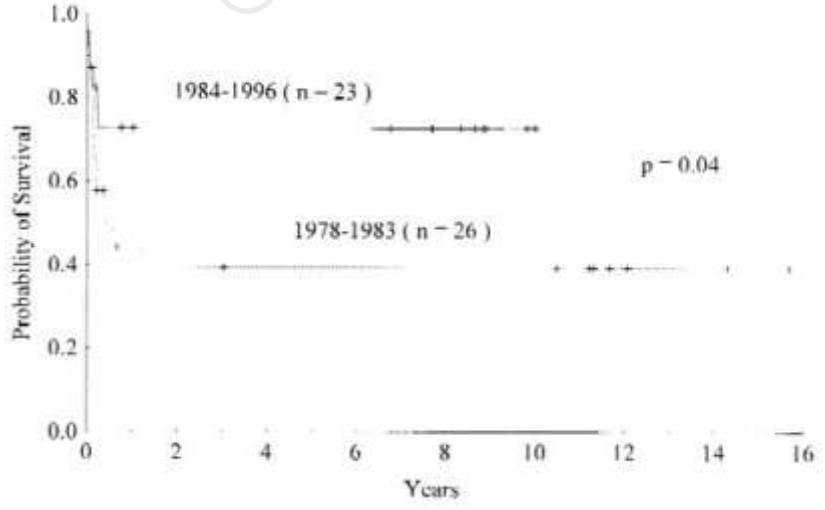

Figure 1. Survival of patients with aplastic anemia given an HLA-identical marrow transplant. Survival of 26 patients transplanted between 1978 and 1983 is compared with that of 23 patients transplanted between 1984 and 1996.

Table 3. Variables of prognostic significance for survival in univariate analysis.

Variable	*Alive/total (%)**	*p*
Patient's age		
≥ 30 years	2/9 (22%)	0.007
< 30 years	26/40 (65%)	
Sex mismatch		
Female to male	8/18 (44%)	0.09
Others	20/31 (65%)	
Interval diagnosis-BMT		
≥ 2 months	11/27 (41%)	0.01
< 2 months	17/22 (77%)	
No. previous transfusions		
≥ 10 units	19/39 (46%)	0.01
< 10 units	9/10 (88%)	
Refractoriness to platelets		
Yes	1/7 (14%)	0.02
No	27/42 (64%)	
GvHD prophylaxis		
MTX	11/25 (44%)	0.08
CSA	17/24 (71%)	
Plasmapheresis		
Yes	2/8 (25%)	0.02
No	26/41 (63%)	

**Probability of survival.*

(median, 1.5) post-transplantation. Primary causes of death were severe acute GvHD (n = 6), graft failure (n = 4), infection (n = 4), hemorrhage (n = 3), chronic extensive GvHD (n = 2), VOD (n = 1) and cardiac arrest (n = 1). In univariate analysis (Table 3), pretransplant factors correlated with survival were patient´s age, male recipients from female donors, interval from diagnosis to transplant, number of previous transfusions, refractoriness to random donor platelets, type of prophylaxis against GvHD and the use of plasma-exchange in ABO mismatch. Previous treatments, etiology or severity of the aplasia, ABO mismatch, preparative regimen with or without irradiation, marrow cell dose, performance status at BMT and infection or liver impairment in the week before the transplantation did not significantly affect survival. In multivariate analysis, three independent factors adversely influenced survival: a) age ≥ 30 years (p = 0.05); b) ≥ 10 transfusion units pre-BMT (p = 0.008); and c) the use of long course MTX for GvHD prophylaxis (p = 0.01) (Table 4). Among patients transplanted after 1984 all of them receiving CSA as GvHD prophylaxis, patient age ≥ 30 years and ≥ 10 transfusion units pre-BMT were both associated with a decreased survival (50 vs 77% and 68 vs 100%, respectively). However, these differences in survival probability did not reach statistical significance due to the small number of patients in each category.

On long-term follow-up, most patients returned to their normal activities and signs of chronic GvHD diminished with time except in three patients; one of them developed severe obliterative bronchiolitis, another had progressive scleroderma and the third had a residual hemiplegia secondary to CNS tuberculosis infection. Two patients were infected with hepatitis C virus. Only one patient developed a secondary malignant condition, namely a squamous-cell carcinoma of the mouth thirteen years after transplantation. This patient had received CY and TAI as the conditioning regimen and developed extensive chronic GvHD that required prolonged treatment with corticosteroids and azathioprine.

Discussion

We report the outcome of 49 consecutive patients with SAA treated with BMT in a single Institution from 1978 to 1996. In 1985 we published the results of the first 27 patients of this series when the actuarial probability of survival was 32%.[26] In contrast, in the present analysis the probability of survival has increased to 55%. This improvement is attributable to the better results obtained after 1984 where the probability of survival is as high as 70%. Similar improvements in the prognosis of transplanted patients with SAA have been reported by other groups,[1,9] and probably reflects diverse factors such as an increase in the experience of the BMT groups, better patient selection, improved transfusional policies, and changes in the preparative regimens.

In the present study three factors were shown to adversely affect survival, namely age ≥ 30 years, transfusion of ≥ 10 units pre-BMT, and the use of long course MTX instead of CSA for GvHD prophylaxis. The deleterious effect on survival of increasing patient age has been noted in many studies. Thus, according

Table 4. Summary of multivariate analysis for survival.

Variable	*Favorable*	*Non favorable*	*RR (CI)**	*p*
Patient age	< 30 yrs.	≥ 30 yrs.	2.60 (1.03-6.58)	0.05
No. previous transfusions	< 10 units	≥ 10 units	7.97 (1.04-60.82)	0.008
GvHD prophylaxis	CSA	MTX	0.31 (0.12-0.80)	0.01

**Relative risk (95% confidence interval). CSA: cyclosporin A; MTX: methotrexate.*

to the *International Bone Marrow Transplant Registry*, between 1986 and 1992 survival of patients more than 25 years of age was less than 60%, whereas for children less than 16 years old it was about 75%.[27] The poorer survival in older patients has been generally related to an increased risk of GvHD. In our series, the group of nine patients age 30 or more had a survival of only 22%, this being mainly due to early deaths and to a higher incidence and severity of GvHD.

Pretransplant transfusions of blood products and subsequent sensitization to minor histocompatibility antigens is considered a major cause of graft rejection.[28,29] However, the number of blood units required to induce allosensitization and compromise the graft is unknown. Therefore, there is no general agreement on a definition of *untranfused* patients carrying a low-risk of graft failure.[1] Since all of our patients had received transfusions before transplant, we arbitrarily chose the level of 10 transfusion units to try to define different risk groups for survival and found that *untransfused* patients had a survival of 88% vs 46% for those *transfused* (p = 0.01). This emphasizes the need for quick referral of patients who have an HLA-identical sibling to transplant centers before they become immunized.

In 1983 and almost simultaneously, the use of CSA and TAI was introduced in the preparative regimen for transplantation in our Institution. Because of this the individual effect of each, one on transplant outcome is difficult to determine. Notably, a marked decrease in the incidence of graft failure was achieved (36% vs 0%, p = 0.004) although this was counterbalanced in part by an increased incidence of grade II-IV acute GvHD (36% vs 44%, p = NS). CSA prophylaxis appears to decrease the incidence of graft rejection[17,30] and that of acute and chronic GvHD,[12,16,27,31] thus increasing survival. On the other hand, the use of irradiation is controversial since the effect in lowering graft failure is offset by a higher incidence of GvHD with no significant influence in survival.[11,12] Concern has been raised regarding the role of irradiation on the incidence of secondary solid tumours.[13,32] We have found only one case of a solid tumour among the 27 patients treated with TAI. This patient had received azathioprine for treatment of extensive chronic GvHD. Recently, the results from the combined experience from Seattle and Paris Institutions showed the complex interactions of potential risk factors for tumor development in patients transplanted because of SAA.[33] In that analysis chronic GvHD and its treatment with azathioprine and the use of irradiation as part of the conditioning regimen had a strong impact on the occurrence of post-transplantation solid tumours. Although it seems that the utilization of regimens including irradiation should be precluded in *untransfused* patients, its role in the context of heavily transfused patients should be studied further, since an incidence of graft failure of about 20% has been reported with conditioning regimens containing CY alone.[21]

In conclusion, this study reinforces the notion that BMT is an effective treatment for young patients with SAA who have an HLA-identical sibling donor particularly if they have been minimally transfused pretransplantation. The poorer results in older patients are in line with other reports[3,10,12,27] and more likely to be due to the presence of adverse prognostic factors, a higher incidence of transplant-related complications, as well as a longer interval from diagnosis to transplant. Finally, it is worth emphasizing that the introduction of thoracoabdominal irradiation and cyclosporin A to our preparative regimen has led to a remarkably increased survival with low risk of long-term sequelae.

Contributions and Acknowledgments

JCHB contributed along with PM to the study design, collected and analyzed the data, and prepared the first draft of the paper. PM had the initial idea of performing this study. He contributed to the study design, interpretation of the data and writing of the manuscript. EC was responsible for the transplant procedure, collaborated in the statistical analysis, and reviewed the paper. JLA was the pathologist who reviewed all the morphologic pictures. AG contributed to the design of the study and clinical management of the patients. CR approved the different protocols and revised their development. EM critically corrected the different versions of the manuscript.

The order takes into account the time spent and scientific contribution of all authors the first author being the idea promoter and the last the senior member of the research group.

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Disclosures

Conflict on interest: none.

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Manuscript processing

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