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Outcomes of Delayed HLA Haploidentical Transplantation with Peripheral Blood Allografts for High-Risk Patients with Severe Aplastic Anemia

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ABSTRACT

Background: In severe aplastic anemia (AA) sibling haploidentical hematopoietic stem cell transplantation (haplo-HSCT) from the peripheral blood (PB) is an alternative when an HLA-identical donor is unavailable. **Objective:** To document the results of haplo-HSCT in high-risk severe AA. **Methods:** Twelve patients with severe AA who failed medical therapy and received a haploidentical PB unmanipulated HSCT from a sibling at an academic medical center were analyzed. Overall (OS) and event-free survival (EFS) were determined by Kaplan-Meier analyses. **Results:** The median between AA diagnosis and haplo-HSCT was 6.5 months (2-19). Median of age was 25.5 (range, 4-54) years; 9 (75%) recipients were males, and all suffered multiple treatment failures. Anti-thymocyte globulin-based conditioning regimens were given to 6 (50%) patients. Five (41.7%) HSCT were ambulatory. Infections developed in all patients and graft failure in 9 (75%). 2-year OS was 52% and EFS 25%. High transfusion burden, treatment failure, and donors > 30 years had no effect on OS ($p = 0.518$, $p = 0.984$, $p = 0.321$) or EFS ($p = 0.113$, $p = 0.692$, $p = 0.199$). Patient's age > 40 was not significant for survival ($p = 0.395$). Three of five evaluable patients developed acute graft-versus-host disease that progressed to chronic disease. **Conclusions:** Delayed PB haplo-HSCT for severe AA offered poor outcomes. Rapid referral for HSCT is critically required. (REV INVEST CLIN. 2025;77(1):26-33)

Keywords: Severe aplastic anemia. Hematopoietic stem cell transplant. Haploidentical transplant. Outpatient hematopoietic stem cell transplantation. Anti-thymocyte globulin. Peripheral blood transplant.

INTRODUCTION

Optimal frontline treatment for severe aplastic anemia (AA) is bone marrow (BM)[1] or peripheral blood[2] hematopoietic stem-cell transplantation (HSCT) from an HLA-matched sibling donor (MSD) using an anti-thymocyte globulin (ATG)-based conditioning regimen. In the absence of an HLA-identical sibling donor, a matched unrelated donor (MUD) is to be considered[3]. Haploidentical hematopoietic stem cell transplantation

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(Haplo-HSCT) from a sibling donor for patients without a MSD represents a valid option in these circumstances[4].

In low- and middle-income countries (LMIC) diverse restrictions prevent patients with severe AA to access optimal treatment, leading to delayed diagnosis and referral to transplant centers[5]. Public healthcare systems that are poorly financed make ATG out of reach for most AA patients. Due to the lack of a national donor network, MUD HSCT is not available for most of these patients, and living in low-income populations prevents HLA-identical allografting if the patient lacks an MSD[6]. In these conditions, sibling haplo-HSCT with or without ATG conditioning regimens can be the only curative option for individuals suffering severe AA. This transplant approach in refractory patients, employing reduced-intensity conditioning, with the PB as the graft source, has been reported to give good results[7].

Studies from LMIC reporting outcomes of haploidentical allografting for severe AA after unsuccessful previous treatment where the source of the graft is T-cell replete PB are scarce[8].

Therefore, we report our experience transplanting patients with severe AA using haploidentical, unmanipulated, non-T-cell depleted, PB in a single-center HSCT program.

METHODS

Patients

Twelve haploidentical transplants in patients with severe AA were carried out at the Hematology Department of the Dr. José Eleuterio González University Hospital, and at the School of Medicine of the Universidad Autónoma de Nuevo León, a public hospital for open-population, low-income uninsured patients from Northeast Mexico. All patients met the criteria for AA[3], received an HLA haploidentical HSCT from a sibling donor using granulocyte colony-stimulating factor (G-CSF) mobilized, T-cell replete, PB as the hematoprogenitors graft source between 2016 and 2020. All patients had complete medical and electronic files available. The institutional Ethics and Research Committees approved the study, waiving an informed consent due to its retrospective design.

Conditioning regimen and graft-versus-host disease (GvHD) prophylaxis

Haplo-HSCT recipients' conditioning scheme consisted of CY (500 mg/m^2/3 days) and Flu (25 mg/m^2/3 days), followed by rabbit ATG (2.5 mg/kg/2 days). Patients who did not have access to ATG received CY (350 mg/m^2/days −3, −2 and −1), Flu (25 mg/m^2/days −3, −2 and −1), and CY (50 mg/kg/days −2 and −1). GvHD prophylaxis included PT-CY (40 mg/kg/day) on days +3 and +4, mycophenolic acid (2 g/day) on days +5 to +30, and oral CsA at 5 mg/kg on day −1[9]. Oral CsA continued for 1 year and adjusted to a target level of 150-250 ng/mL. The hematopoietic allograft was infused on day 0. Antimicrobial prophylaxis included oral levofloxacin 500 mg, oral itraconazole 100 mg, and acyclovir 400 mg daily until engraftment. After the engraftment, trimethoprim substituted with levofloxacin until immunosuppressive treatment was halted. Transplants were carried out in the outpatient hematology clinic if the patient was considered fit for procedures in this setting, including administration of the conditioning regimen, central venous catheter placement, and allograft infusion. Patients were admitted to the hospital in the event of severe post-HSCT complications.

Definitions

The AA severity was classified according to Camitta et al.[10] criteria. Neutrophil engraftment was defined as an absolute neutrophil count (ANC) of > 0.5 × 10^9/L for 3 consecutive days unsupported by G-CSF. Platelet engraftment was when platelets (PLT) reached >20 × 10^9/L for at least 7 consecutive days without transfusion support. Minor ABO incompatibility was defined as donor isoagglutinins in the plasma specific for the recipient's red blood cells (RBCs). Major incompatibility was defined as recipient plasma isoagglutinin's incompatible with the donor RBCs. Primary graft failure (GF) was defined as neutrophil engraftment failure by day +28, and secondary GF as a drop in ANC < 0.5 × 10^9/L after initial engraftment with loss of donor chimerism. The transplant was ambulatory if the conditioning regimen and stem cell infusion were performed in the outpatient clinic. Transplant-related mortality (TRM) was defined as death not caused by relapse or progression. Transplant-related hospitalization was any event requiring inpatient care within day +1 to day +100 in the

post-HSCT period. Overall survival (OS) was measured from the date of allografting to the date of death, and event-free survival (EFS) from the date of transplant to graft failure (GF) or death. Diagnosis of acute (aGvHD) and chronic GvHD (cGvHD) were made according to standard NIH criteria[11]. GvHD grading systems were Glucksberg for aGvHD and NIH consensus criteria for cGvHD[12]. A complete response required normalization of all blood counts (hemoglobin [Hb] level, > 13 g/L, ANC > 1.5 × 10^9/L, and platelet count, > 125 × I0^9/L). All others were classified as non-responders[13].

Transfusion support

Packed RBC (PRBC) transfusion was provided for patients with anemic syndrome or with a Hb concentration < 8 g/dL in patients with cardiopulmonary disease. PLT were prophylactically transfused when the PLT count was < 10 × 10^9/L, with a higher threshold of 20 × 10^9/L for patients with mucocutaneous bleeding or fever. A high pre-HSCT transfusion burden required more than 20 transfusion episodes of PRBC, PLT, or both combined.

Statistical analysis

SPSS version 25 (IBM SPSS Statistics software, IBM Corp., Armonk, NY) was used for data analysis. Categorical variables were displayed as absolute numbers and percentages and were made with the Pearson x^2 test. Quantitative variables were analyzed with descriptive statistics, including median and ranges. The Mann-Whitney U test was used to compare quantitative variables. OS was measured from the time of transplantation to the time of death or last visit. EFS was measured from the date of transplantation to the time of relapse, death, or last visit employing the Kaplan–Meier method was employed to estimate OS and EFS. A $p < 0.05$ was considered statistically significant.

RESULTS

Twelve haplo-HSCTs were carried out in severe AA patients during the study period. The median follow-up was 15 (3-34) months. Median age at transplantation was 25.5 (range, 4-54) years and 9 (75%) patients were males. At the time of transplantation, all patients had failed previous drug treatment. Initial therapy for 5 (41.6%) patients consisted of cyclosporine, for 2 (16.6%) it was danazol alone, and 5 (41.6%) received both. The median time from AA diagnosis to referral for HSCT was 6.5 months (2-19) and 6 (50%) patients had more than 6 months of evolution.

Regarding transfusion support episodes before transplantation, 10 (83.3%) patients received 20 or more PRBC; 1 (8.3%) required platelet transfusion on 20 or more occasions. Additional baseline characteristics are shown in table 1.

Transplant-related characteristics

Five (41.7%) transplants were performed in a completely ambulatory setting, whereas 7 (58.3%) required hospitalization to administer the conditioning regimen and/or the stem cell infusion. The median donor age was 35 (5-53) years, and 41.7% of the donors were < 30 years. Six (50%) patients received ATG-based conditioning regimens. Table 2 displays additional HSCT-related features.

Engraftment

For 5 evaluable patients, the median time from HSCT to neutrophil engraftment was 14 (12-17) days, while for platelet engraftment it was 15 (14-20) days.

GvHD and transplant-related complications

At a median time of 32 (18-45) days post-transplantation, 3 (60%) of 5 evaluable patients developed aGVHD, grade II in one and grade III in two. The 3 progressed to cGVHD at a median time of 4 months; it was moderate in severity, and the main locations included the skin and oral cavity, with discrete liver and gastrointestinal involvement. After 4 weeks at a steroid dose of ≥ 1 mg/kg/day, a favorable clinical response was attained.

Infections developed after all 12 transplants, and 10/12 (83.3%) required hospitalization for treatment administration. The main causes for hospitalization were neutropenic fever (n = 6), Cytomegalovirus colitis (n = 3), and acute transfusion requirements (n = 1). Additional transplant-related complications are presented in table 3.

Table 1. Baseline characteristics of 12 patients with severe aplastic anemia receiving an HLA-haploidentical transplant at a hematology referral center in Northeast Mexico. All donors were siblings, and the hematopoietic graft was obtained from G-CSF mobilized peripheral blood

Variable	n = 12
Age at HSCT, median (range), years	25.5 (4-54)
Recipient, n (%)	
Female	3 (25)
Male	9 (75)
Severity, n (%)	
Moderate	1 (8.3)
Severe	11 (91.7)
Very severe	0 (0)
Time from diagnosis to transplant, median (range), months	6.5 (2-19)
Packed Red Blood Cells transfusion episodes, n (%)	
< 20	2 (16.7)
> 20	10 (83.3)
Platelet transfusion episodes, n (%)	
< 20	6 (50)
> 20	1 (8.3)
Treatment lines pre-HSCT, n (%)	
1 line	6 (50)
2 lines	4 (33.3)
3 lines	2 (16.7)
Therapy received pre-HSCT, n (%)	
Danazol	7 (58.3)
Alemtuzumab	0 (0)
Cyclosporine	10 (83.3)
Anti-thymocyte globulin	3 (25)
Eltrombopag	1 (8.3)
Intravenous immunoglobulin	3 (25)
Monoclonal antibodies	0 (0)
Erythropoietin	2 (16.7)
Steroids	6 (50)
HSCT[§]	1 (8.3)

HSCT: hematopoietic stem cell transplantation. G-CSF: granulocyte colony-stimulating factor.

Graft failure and transplant-related mortality

Nine (75%) procedures resulted in GF; primary GF occurred in 7 (58.3) cases and secondary GF in 2 (16.7%) after developing sepsis. Transplant-related deaths occurred in 5 (41.7%) recipients. Specific HSCT complications are shown in table 3. Four patients

Table 2. Salient characteristics of 12 hematopoietic transplants in severe aplastic anemia patients. All grafts were obtained from the unmanipulated peripheral blood of sibling donors after G-CSF mobilization

Variable	n = 12
Transplantation setting, n (%)	
Ambulatory	5 (41.7)
Inpatient	7 (58.3)
Donor-recipient sex mismatch, n (%)	
Female-male	2 (16.7)
Male-female	0 (0)
No mismatch	10 (83.3)
Unknown	0 (0)
ABO mismatch, n (%)	
Major	1 (8.3)
Minor	1 (8.3)
Mixed	0 (0)
No mismatch	10 (83.3)
Unavailable donor data	0 (0)
Conditioning	
ATG-based regimens	6 (50)
Non-ATG-based regimens	6 (50)
CD34+ dose ($\times 10^6$/kg), median (range)	5.9 (1.17-18.6)
Neutrophil engraftment, days, median (range), n = 5	14 (12-17)
Platelet engraftment, days, median (range), n = 5	15 (14-20)

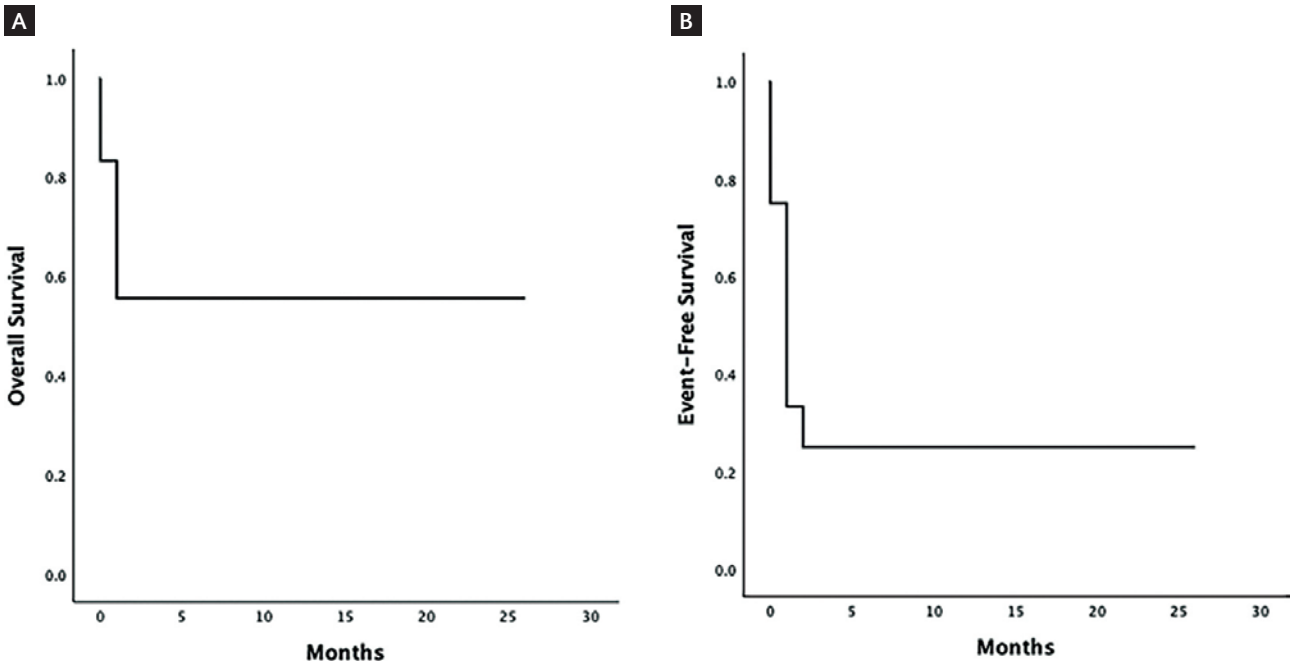
ATG: anti-thymocyte globulin. BM: bone marrow. HSCT: hematopoietic stem cell transplantation. PBSCs: peripheral blood stem cells. G-CSF: granulocyte colony-stimulating factor.

Table 3. Haploidentical hematopoietic stem cell transplant related complications after haploidentical allografting in high-risk patients with severe aplastic anemia. The donor was a sibling in all cases and the T-cell replete graft was obtained from the peripheral blood

HSCT-related complications	n = 12 (%)
Infections	12 (100)
Cytomegalovirus	3 (25)
Aspergillus	3 (25)
Bacterial	3 (25)
Missing	3 (25)
Mucositis	1 (8.3)
Neutropenic fever	7 (58.3)
Primary graft failure	7 (58.3)
Secondary graft failure	2 (16.7)
Acute GvHD	3 (25)
Chronic GvHD	3 (25)
Transplant-related mortality	5 (41.7)

GvHD: graft-versus-host disease, HSCT: hematopoietic stem cell transplantation.

Figure 1. **A:** overall survival and **B:** event-free survival for patients with severe aplastic anemia who underwent HLA haploidentical hematopoietic stem cell transplantation from the peripheral blood of sibling donors.



suffering primary GF died, while 3 are alive and on danazol therapy. One patient suffering secondary GF was lost to follow-up, and 1 received a second transplant, and is alive.

Outcomes and survival

The 2-year OS was 52% (95% CI 48.66-5504) and the 2-year EFS was 25% (95% CI 49.76-57.08) for the whole cohort, respectively (Figs. 1 and 2). Patients with high transfusion burden (>20 transfusion episodes pre-HSCT, treatment failure before transplantation, and recipients that received grafts from donors >30 years old were not significant (p = 0.518, p = 0.984 and p = 0.321, respectively). Having received immunosuppressive therapy with ATG before HSCT (p = 0.115) and using ATG-based conditioning regimens (p = 0.538) did not appear to improve OS in the transplant recipients.

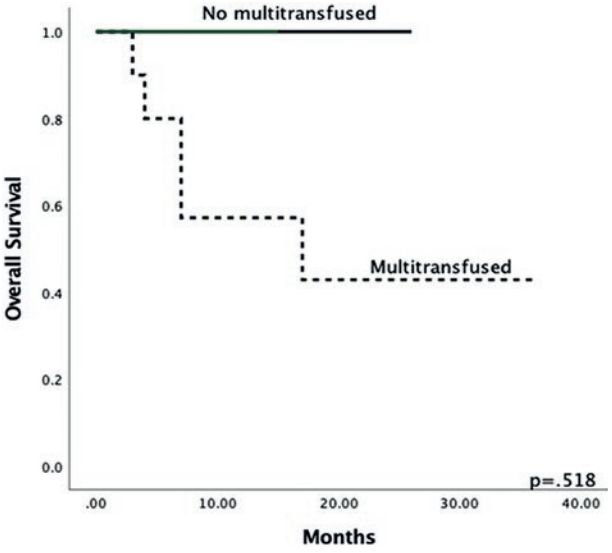
The ≤ 18-year patient group (n = 5) did not show significant differences in OS or EFS compared to the patients > 18 years (n = 7) (p = 0.882 and p = 0.982, respectively). Donor age > 30 years was not associated with an inferior OS (p = 0.321).

Donor-specific antibodies (DSA) results were available for 6 patients receiving a haploidentical allograft, being positive in 3 (50%); the DSA were specific against HLA donor's antigens, with mean fluorescence intensity of 13,352, 3,714, and 15,275, respectively.

DISCUSSION

Donor availability is a significant limitation for severe AA patients and is pronounced in developing countries without a structured national donor network. Most of our patients were not diagnosed at our institution but were referred after a median time of 6.5 months from diagnosis to transplantation, compared to < 3 months in developed countries[14]. All patients in this report received pharmacologic therapy as first-line treatment, more frequently cyclosporine and danazol; danazol offers 41% of OS at 10 years[15], while in this same population, HLA-identical HSCT from a sibling has a survival probability of 81% in the long term[16]. Due to financial restrictions, rabbit ATG in the conditioning regimen was used only in half of the study patients; its equine alternative is not available in our country. These factors resulted in a high-risk severe

Figure 2. Overall survival for patients with aplastic anemia who received a HLA haploidentical transplant from the peripheral blood of sibling donors, according to more or less 20 pre-transplant transfusion episodes.



AA patient cohort. Importantly, MSDs as well as alternative donor transplantation as first-line treatment achieve superior outcomes compared to immunosuppressive therapy (IST)[4,17,18].

In addition to the small number of patients leading to non-significant statistical differences, our results appear to have been influenced by the prolonged time elapsed between severe AA diagnosis and transplantation, and the fact that only half of the patients received ATG in the conditioning regimen. Although there are different reasons for the lack of expedited access to transplantation in our population, the major factor is the restricted financing allocated for dealing with catastrophic diseases, such as severe AA[6]. Our country faces significant healthcare infrastructure limitations, budgetary restrictions, lack of trained personnel, and scarcity of transplant centers, issues common to other low- and middle-income countries[9,19,20]. A prolonged time to transplantation in patients with severe AA has been reported from other low-income countries[21,22], as well as in a developed nation[23,24].

ATG was used only in half of our patients, which might in part contribute to explaining the unusually high rate of GF; it has been reported that administration of ATG at this time reduces this risk[12,25]. Although Alemtuzumab can be used for T-cell depletion, at present its availability is limited[25,26]; post-transplant cyclophosphamide represents a practical and affordable approach for controlling T-cell response after HSCT[27-29], and its use during prophylaxis in haploidentical transplantation has been reported to increase survival due to reduced GvHD incidence and severity[30].

The age of the recipient at the time of transplant plays an important role in survival, and patients < 40 years have the best outcomes[1,31]; in this regard, guidelines favor IST in patients > 35-50 years[3]. No age-related differences were found in our small cohort, suggesting that older patients might be considered as transplant candidates in the absence of ATG; to confirm this, a sufficiently powered prospective study would be required.

MUD allografting represents an alternative transplant modality for severe AA patients who lack an HLA-identical family donor; however, like in numerous developing populations, no national donor network exists in our country, and the use of CD34+ cell products from other countries is halted by its high costs. Our results also reflect the earlier stages in the implementation of technology, lack of total body irradiation, variable ATG availability, limited access to anti-HLA DSA assay and desensitization therapy for positive cases, as we are in the learning curve for haplo-HSCT from PB in severe high-risk AA cases. To improve the results reported here, DSA testing is currently being carried out in all patients, and the desensitization protocol has improved incorpotating daratumumab plus bortezomib.

Remarkably, a high rate of primary GF affected this haplo-HSCT cohort, which could have been related to anti-HLA DSA presence; however, the assay was performed only in one-half of the patients, who must pay out-of-pocket for the test. Other experiences have shown similar challenges with the initial use of this transplant modality[32]. In contrast, a recent phase 2 trial in 27 newly diagnosed patients in the United States has shown promising results with a strategy that incorporates haploidentical transplantation upfront with non-myeloablative conditioning with ATG, fludarabine, cyclophosphamide, and 4 Gy of total body irradiation, achieving a 92% OS at 3 years[33]. Favorable outcomes in children have also been reported with initial experiences by investigators in Mexico and India[34,35].

A second haploidentical bone marrow transplant (BMT) with an ATG-based conditioning regimen for saving 8 severe AA patients with GF was recently reported. The median CD34+ dose was 6.2×10^6/kg. All patients were engrafted at a median of 12.5 days for neutrophils and 24 days for PLT. Six patients survived with an estimated 5-year OS of 75% and a median follow-up of 61 months[36]. Due to the cited limitations, only one patient suffering from GF in our group received a second transplant; the others received pharmacologic therapy.

Haplo-HSCT from PB was carried out in all patients, this approach represents considerable savings in the cost of the procedure and is also associated with faster myeloid and platelet recovery[37]. Using PB as the source of the graft demands less time for the transplant team, and no need for anesthesia or a surgery room, leading to considerable financial savings for patients who must pay out of pocket for their transplant[38-40]. BM is the best graft source in severe AA patients, requiring a BMT unit, unavailable in most low-income populations; in a multicenter study including 31 patients with relapsed or refractory severe AA allografted with BM, the 1-year OS was 81%[30].

Most (10/12) of our patients received more than 20 PRBC pretransplant transfusions and this could be related to lower OS, probably related to HLA-sensitization, although no statistical analysis could be done due to the reduced sample size.

The main limitations in our retrospective study include but are not limited to, a short follow-up and the small number of patients. However, the study identifies the main problems encountered when performing delayed sibling haplo-HSCT using non-T-cell depleted allografts from PB in high-risk, severe AA multitransfused patients with limited resources in LMIC.

In conclusion, haploidentical sibling donor HSCT with unmanipulated grafts from PB is a valid option for high-risk severe AA patients living in resource-limited settings where HLA-identical donors, ATG, and a BMT unit are not available; in these circumstances, shortening the time between severe AA diagnosis and early referral for HSCT, inclusion of DSA testing for donor selection, and the use of an appropriate conditioning scheme, like the one reported by Dezern[33], are unmet needs requiring urgent attention.

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