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ORIGINAL ARTICLE

DESENSITIZATION THERAPY FOR ELEVATED DONOR-SPECIFIC ANTIBODY LEVELS IN HAPLOIDENTICAL TRANSPLANTATION IN CHILEAN PATIENTS

Sarmiento M[1], Salinas J[1], Rojas P[1], Gutierrez C[1], Vidal M[1], Jara V[1], Garcia MJ[1], Campbell MJ[1], Flores Y[1] Sandoval V[1], Vergara M[1], Palacios F[1], Ocqueteau M[1]

1 - Programa de trasplante hematopoyético del adulto. Red de Salud Christus UC - Pontificia Universidad Católica de Chile.

Corresponding author: Mauricio Sarmiento (E-mail: msarmiento@ucchristus.cl)

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ABSTRACT

Allogeneic stem cell transplantation (ALOSCT) is curative for several hematological diseases. Unrelated donors and cord blood stem cells are valid options but haploidentical donors (HAPLO) have been considered the main source of stem cells in several countries, partly due to easy access and low cost of the transplantation process. Unfortunately, some patients have antibodies against the HLA epitopes from family haploidentical donors (donor-specific antibodies [DSA]) which are associated with engraftment failure and lethality. A few strategies exist to reduce or eliminate HLA antibodies that bind to these receptors. In this study, we present our experience with DSA desensitization by retrospectively examining a cohort from our hospital program. Between 2012 and 2023, we performed 243 ALOSCTs, of which 142 were from HAPLO and 56 were from unrelated donors. Nine patients (7%) had elevated DSA levels, most of which were female patients and mostly HAPLO. The median fluorescence intensity for these patients was 22,490 (19,000-28,560). Most of these high DSA patients (80%) received a desensitization procedure that involves plasmapheresis, rituximab, and immunoglobulin. The remaining 20% had severe infections during transplantation, and received rituximab monotherapy instead. The median dose of stem cells infused was 6.5 x 10^6 CD34/kg. Graft-versus-host disease (GVHD) preventative measures for all patients involved post-transplantation cyclophosphamide. Primary graft failure was observed in 45% of DSA elevated patients. For the remaining patients, median granulocyte and platelet engraftment were 14 d (12-16) and 16 d (13-18), respectively. Mortality in patients who did not receive engraftment was 100%. The incidence of mild, chronic GVHD was 15%. In conclusion, the desensitization of DSA in patients provided a 55% rate of engraftment and survival. However, a 45% rate of primary graft failure continued to pose a challenge in patients with DSA and required the development of improved strategies to reduce elevated transplant-related mortality.

Keywords: Stem Cell Transplantation. Allogeneic Cells. Desensitization, Immunologic. Antibodies.

INTRODUCTION

Allogeneic stem cell transplantation (ALOSCT) is a curative treatment option for many diseases[1]. Before the year 2000, patients without family donors or access to cord blood grafts could not receive stem cell transplants. Over the last few decades, haploidentical donors (HAPLO) have emerged as a relevant source of stem cell precursors, providing access to transplantation for many patients (1). However, since the development of the HAPLO platform and unrelated donors (URD) availability, primary graft failure (PGF) has been a frequent challenge[2-3]. Cut-off values for donor-specific antibodies (DSA),

which are measured by median fluorescence intensity (MFI) >10,000, were established as a risk factor for PGF. Ciurea et al. reported DSA as contributors to PGF and provided a desensitization strategy with a 50% success rate[4]. Similarly, reports suggest that patients who receive a pre-transplant plasmapheresis, followed by rituximab and high-dose IVIG, have a 50% reduction in DSA levels. Based on this data, our adult transplantation program began with HAPLO in 2012 and utilizes this desensitization procedure in patients with high titers of DSA. Here, we report our experience with patients from a Latin American transplantation center.

PATIENTS AND METHODS

Patients

Since 2012, our institution started using HAPLO donors for adult allogenic hematopoietic stem cell transplantation. The cyclophosphamide post-transplantation strategy was adopted according to validated protocols[5]. For this study, we performed a retrospective analysis of all patients transplanted since 2012 and collected data regarding demographics, transplantation procedures and clinical outcomes.

Conditioning

Our institutional guidelines offer myeloablative transplantation in fit patients under 45 years of age. Cyclophosphamide/total body irradiation or fludarabine/total body irradiation were used. Patients unfit for myeloablation were treated with reduced-intensity conditioning such as fludarabine in combination with melphalan, busulfan, or cyclophosphamide.

Transplantation procedures

All patients received a detailed pre-transplant evaluation measuring global functions. Our program performs hospitalized transplantations. Immunosuppressor monitoring and the administration of granulocyte-colony stimulating factor (G-CSF), antibiotics, antifungals, antiviral prophylactics, and related treatments are standardized according to institutional guidelines and were reported previously[6].

DSA testing

In all HAPLO patients, DSA tests were performed during pre-transplantation screening. According to the Luminex technique, blood samples with EDTA were processed with the fluorometric, solid phase immunoassay for individualized HLA-purified class I and II antigens. A MFI >10,000 DSA units was designated as positive for graft failure risk.

Desensitization strategy

In patients with DSA-positive tests, a desensitization protocol with the standard desensitization therapy was administered (Figure 1). The procedure started one week before conditioning and consisted of three sessions of plasmapheresis with 1× to 1.5× plasma volume (replaced with either fresh or frozen plasma) followed by rituximab 375 mg/m^2 and administration of immunoglobulin 2 gr/kg over two days.

Graft-versus-host disease (GVHD) prophylaxis

In all HAPLO patients, post-transplantation cyclophosphamide was administered at a dose of 50 mg/kg on days 3 and 4. Subsequently, tacrolimus and mycophenolate were administered and progressive discontinuation started at 4 months post-transplantation, for those who tolerated the treatment.

GVHD treatment

Institutional guidelines for GVHD treatment start with the adjustment of immunosuppressors, topical corticosteroids, and systemic methylprednisolone. If there was no response, ruxolitinib, vedolizumab, ibrutinib, or extracorporeal photopheresis were available[7].

Ethics aspects

The studies involving human participants were reviews and approved by clinical ethic committee of the Hospital Universitario de la Pontificia Universidad Católica de Chile. All patients provided written, institutional informed consent permitting the collection of anonymous data and transplantation outcomes. The institutional ethics board approved publication of this data.

Statistical methods and outcome definitions

The demographic and baseline characteristics were presented using mean, percentage, and ranges. Transplantation outcomes are analyzed in a frame of competitive risk and cumulative incidence. The comparisons between the variables were made with the Chi-square method. The survival probabilities were estimated with the Kaplan–Meier method. Engraftment was defined was defined as the first of three consecutive days of achieving a sustained peripheral blood neutrophil count of >500 × 10^6 /L and independence from platelet transfusion for at least 7 days with a platelet count of more than >20 × 10^9/L Primary graft failure was established when there was no evidence of neutrophil and platelet engraftment at +30 d. The effects of the events that occurred during the follow-up and after transplantation, such as acute GVHD or relapse, were analyzed as a time-dependent covariate. The SPSS version 15 (IBM Software, USA) and Prisma Software version 6.0.1 (GraphPad Software, USA) were used for analysis. The differences were considered significant for values of $p < 0.05$, with 95% confidence intervals (CIs).

RESULTS

Patients, diseases, and characteristics

Between 2012 and 2023, we performed 243 ALOSCTs, of which 142 were from HAPLO and 52 from full match unrelated donors (URD). Of those, 133 HAPLO and 49 URD patients without elevated DSA levels, did not experience PGF. The remaining 9 patients (7%, DSA >10,000 MFI) were mostly females. In Table 1, demographic and basal characteristics of patients with high DSA levels are summarized.

DSA test and desensitization

The median MFI of patients with high DSA level was 22,490 (12,000-28,560). In (n = 7) 80% of these patients, desensitization therapy involved plasmapheresis, rituximab, and immunoglobulin. In two patients with severe fungal (mucormycosis and aspergillar sp infections respectively) infection at transplantation, desensitization involved rituximab monotherapy (Table 2). There was no correlation between MFI positivity and PGF. The median MFI of the successful engraftment group was 19,283 and in the PGF group was 20,886 (p = 0.9).

Transplantation outcomes

The median stem cell engraftment count (CD34/kg) post-transplant, was 6.5 x 10^6 CD34/kg. PGF was observed in 45% of the patients with high DSA levels. In patients with successful engraftment (55%), granulocyte and platelet engraftment levels reached 66% at medians of 14 d (range 12-16) and 16 d (range 13-18), respectively (Table 2). Acute GVHD grade 3-4 was reported in one patient who was refractory to all treatments. Chronic GVHD was reported in two patients and was limited to mild cutaneous symptoms.

Transplant-related mortality and overall survival

Overall survival at 3 years was 55% with the median not reached (Figure 2). Mortality was 45% (n = 4) all of which were transplant related. Three of the reported deaths were associated with PGF (two with previous AML and one with T-ALL, all heavily treated), and one (previous T-ALL) had hematologic complete recovery but with acute intestinal GVHD, refractory to corticosteroids, ruxolitinib, tocilizumab, mesenchymal stem cells, extracorporeal photopheresis, fecal microbiota transplantation, and infliximab. In patients with PGF, mortality was associated with fungal infections that were unresponsive to medical treatment.

DISCUSSION

Haploidentical donors for allogeneic transplantation have become a cornerstone of hematology, allowing transplantations for patients who would not have qualified decades ago. Since the release of the Luznik et al. HAPLO protocol[8], transplantation institutions worldwide, have successfully adopted HAPLO for transplantation[9]. However, PGF is a frequent occurrence with HAPLO and cord blood transplantations[10]. Reports suggest the incidence of PGF is variable and ranges from 30% to 56%. Our data shows that in a cohort of Chilean patients, mainly with acute leukemia, high DSA levels were associated with PGF and mortality even after desensitization. In our analysis, the MFI intensity was not associated with PGF; however, some patients with a strongly positive MFI had successful engraftments. One disadvantage to our analysis is the retrospective nature of our data and the small sample size. However, when reviewing available data from other previous studies, most were also retrospective and had small patient numbers[4,11,12]. Due to the scarcity of evidence, a meta-analysis was conducted and reported a total of 2,436 patients from 15 studies. This meta-analysis reported that the presence of DSA before ALLOSCT had a 7.47-fold increased risk of PGF failure compared to patients without anti-HLA DSA (OR 7.47; 95% confidence interval, 4.54 to 12.28, P < 0.001; I^2 = 28.91%, P = 0.13). The authors also reported that mean fluorescence intensity cutoff, primary disease, graft source, conditioning, and pre-transplantation desensitization did not affect the rate of PGF. Nonetheless, this meta-analysis included patients with both cord blood and HAPLO transplants, and analyzed mostly non-randomized studies, making it difficult to conclude with certainty[10]. Better quality evidence from randomized studies is difficult to obtain due to ethical considerations; since it would be problematic to propose a study in a control group with DSA and without desensitization. There is no definition of the best desensitization strategy with the same uncertainty. Recently, Ciurea et al. updated data on desensitization with the same strategy used in our program. In a matched case-control study, 37 patients, with a median age of 51 years, were treated with this desensitization protocol and compared to a control group of HAPLO patients without DSAs (n = 345). Mostly in women receiving stem cells from their child, the mean DSA decreased on average from 10,198 to 5,937 MFI. This study also reports that patients with DSA levels at >20,000 MFI and persistent positive C1q after desensitization had a significantly lower engraftment rate, higher non-relapse mortality, and worse overall survival than in the control group[13]. Regarding desensitization, there is a consensus promoting B-cell lymphodepletion. Since starting rituximab in this clinical scenario, several medications have been developed for other diseases related to the proliferation of

B lymphocytes. For example, there are many excellent medications that are used to treat myeloma that consistently reduce antibody production and have attractive mechanisms of action, with a possible use in DSA reduction. The use of daratumumab[14], bortezomib[15], or even other monoclonal antibodies have emerged as possible methods for achieving better desensitization rates in patients with DSA.

CONCLUSION

In our experience, desensitization provides a better chance at successful transplantation in patients with elevated DSA levels. However, ALLOSCT patients still frequently experience PGF and further investigations to identify new strategies to reduce mortality in this group of patients are necessary.

TABLE 1. Patient characteristics

Sex female/male	n = 6 (66%)/ n = 3 (34%)
Age median (range)	40 years (21-47)
Diagnosis (sex)	Acute myeloid leukemia CR 2: n = 3 (female = 2) Acute T lymphoblastic leukemia CR2: n = 2 (female = 1) Acute B lymphoblastic leukemia Philadelphia + CR1: n = 1 (female = 1) Severe aplastic anemia: n = 2 (female = 2) Myelodysplastic syndrome: n = 1 (male = 1)
Pre-transplant treatment	In AML/MDS patients 7/3: n = 1 FLAGIDA: n = 3 Venetoclax/azacytidine: n = 3 In ALL patients BFM: n = 1 HyperCVAD: n = 2 HyperCVAD + Dasatinib: n = 1 ATG/Eltrombopag/Cyclosporine: n = 2
Donor type	Unrelated matched donor n = 3 Haploidentical n = 6
Median fluorescence intensity of donor-specific antibodies (range)	22,490 (12,000-28,560)
Conditioning	Cyclophosphamide/total body irradiation: n = 1 Fludarabine/cyclophosphamide/ATG: n = 3 Fludarabine/melphalan: n = 4 Fludarabine/busulfan: n = 1
AML: acute myeloid leukemia. CR: complete response. ALL: lymphoblastic acute leukemia. MDS: myelodisplastic syndrome. FLAGIDA: fludarabine, citarabine, idarrubicine. BFM: Berlin/Frankfurt/Munster protocol. 7/3: daunorrubicine/cytarabine. ATG: antithymocyte globulin. HyperCVAD: cyclophosphamide, vincristine, doxorrubicina, dexamethasone, citarabine, methotrexate.	

TABLE 2. Transplantation characteristics and outcomes

Median CD34 x 10^6 CD34/kg infused (range)	9 (3.8-11)
Engraftment % and day (range) Granulocytes Platelets	 66% at median day 12 (12-18) 66% at median day 15 (13-18)
Primary graft failure	n = 3 (34%)
Acute graft versus host disease 3-4/100 days	n = 1
Chronic graft versus host disease	n = 2 cutaneous, mild
Mortality and causes primary graft failure refractory acute graft versus host disease	n = 4 (45%) n = 3 n = 1
3-year overall survival	n = 5 (55%)

FIGURE 1. Desensitization strategy.

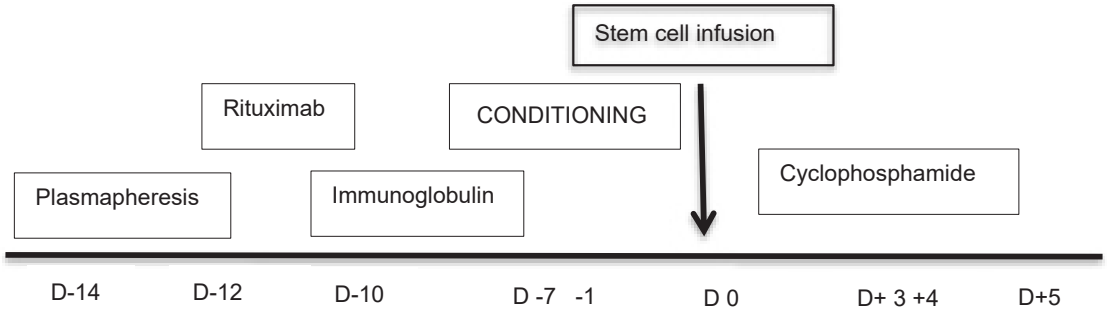
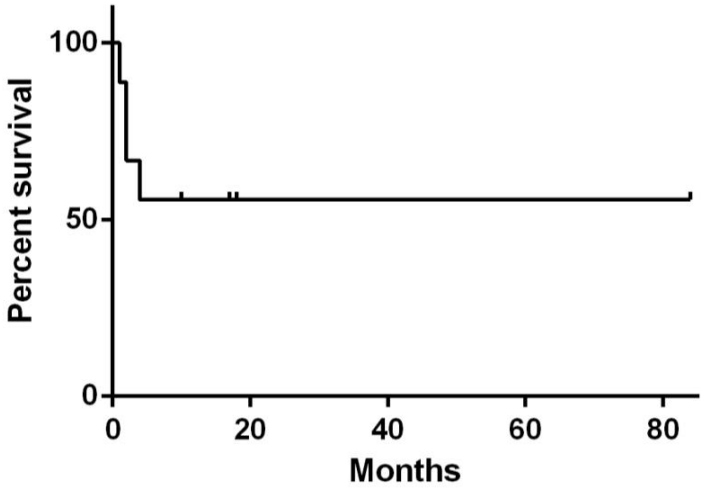


FIGURE 2. Overall survival of patients with DSA who received desensitization therapy



REFERENCES

1. Duarte RF, Labopin M, Bader P, et al. European Society for Blood and Marrow Transplantation (EBMT) (2019). Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. Bone Marrow Transplant. 2019;54(10):1525-52.

2 . Ciurea SO, Cao K, Fernandez-Vina M, et al. The European Society for Blood and Marrow Transplantation (EBMT) Consensus Guidelines for the Detection and Treatment of Donor-specific Anti-HLA Antibodies (DSA) in Haploidentical Hematopoietic Cell Transplantation. Bone Marrow Transplant. 2018;53(5):521-34. Erratum in: Bone Marrow Transplant. 2018 Sep 19.

3. Bramanti S, Calafiore V, Longhi E, et al. Donor-Specific Anti-HLA Antibodies in Haploidentical Stem Cell Transplantation with Post-Transplantation Cyclophosphamide: Risk of Graft Failure, Poor Graft Function, and Impact on Outcomes. Biol Blood Marrow Transplant. 2019;25(7):1395-1406.

4. Ciurea SO, Lima M, Cano P, et al. High risk of graft failure in patients with anti-HLA antibodies undergoing haploidentical stem-cell transplantation. Transplantation. 2009;88(8):1019-24.

5. Robinson TM, O'Donnell PV, Fuchs EJ, et al. Haploidentical bone marrow and stem cell transplantation: experience with post-transplantation cyclophosphamide. Semin Hematol. 2016;53(2):90-7.

6. Sarmiento M, Ramirez P, Jara V, et al. Haploidentical transplantation outcomes are comparable with those obtained with identical human leukocyte antigen allogeneic transplantation in Chilean patients with benign and malignant hemopathies. Hematol Transfus Cell Ther. 2020;42(1):40-5.

7. Triantafilo N, Sarmiento M, Palacios F, et al. Time to Change Our Practice: Experience in the Treatment of Steroid Refractory Graft Versus Host Disease in a University Hospital in Chile. Blood. 2019;134(Supplement 1):5683.

8. Luznik L, Jalla S, Engstrom LW, et al. Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide. Blood. 2001;98(12):3456-64.

9. Nath K, Lee J, Elko TA, et al. Prospective analysis to determine barriers to allogeneic hematopoietic cell transplantation in patients with acute leukemia. Am J Hematol. 2023;98(12):1869-76.

10. Xie Y, Parekh J, Tang Z, et al. Donor-Specific Antibodies and Primary Graft Failure in Allogeneic Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis. Transplant Cell Ther. 2021;27(8):687.e1-7.

11. Zhang R, He Y, Yang D, et al. Combination treatment of rituximab and donor platelets infusion to reduce donor-specific anti-HLA antibodies for stem cells engraftment in haploidentical transplantation. J Clin Lab Anal. 2020;34(7):e23261.

12. Ruggeri, A., Rocha, V., Masson, E., Labopin, M., Cunha, R., Absi, L., ... & Loiseau, P. (2013). Impact of donor-specific anti-HLA antibodies on graft failure and survival after reduced-intensity conditioning-unrelated cord blood transplantation: a Eurocord, Societe Francophone d'Histocompatibilite et d'Immunogenetique (SFHI) and Societe Francaise de Greffe de Moelle et de Therapie Cellulaire (SFGM-TC) analysis. *haematologica*, *98*(7), 1154.

13. Ciurea SO, Al Malki MM, Kongtim P, et al. Treatment of allosensitized patients receiving allogeneic transplantation. Blood Adv. 2021;5(20):4031-43.

14. Ibrahim U, Keyzner A. Daratumumab for donor-specific anti-HLA antibody desensitization in a case of HLA-mismatched allogeneic stem cell transplantation. Hematol Transfus Cell Ther. 2023;45(4):510-2.

15. Horn ET, Xu Q, Dibridge JN, et al. Reduction of HLA donor specific antibodies in heart transplant patients treated with proteasome inhibitors for antibody mediated rejection. Clin Transplant. 2023;37(12):e15132.