



**Research Article**

## **HAPLOIDENTIC TRANSPLANTATION INJURY FAILURE IN A GIRL WITH ACUTE MYELOID LEUKEMIA**

**Pamela Zazueta-Mérida<sup>1</sup>, Yadira Melchor-Vidal<sup>2</sup>, Rocío Cárdenas-Cardós<sup>2</sup>, Haydeé Salazar-Rosales<sup>3</sup>, Nideshda Ramírez-Uribe<sup>3</sup>, Gerardo López-Hernández<sup>3</sup>, Alberto Olaya-Vargas<sup>4</sup> and Roberto Rivera-Luna<sup>5</sup>**

<sup>1</sup>Resident Doctor in Bone Marrow Transplant Unit, ABC Medical Center, Mexico City

<sup>2</sup>Bone Marrow Transplant Unit, ABC Med, Mexico City

<sup>3</sup>Bone Marrow Transplant Unit, Nacional Institute of Pediatrics, Mexico City

<sup>4</sup>Program Director

<sup>5</sup>Director of Hem/Oncology

### **ARTICLE INFO**

**Article History:**

Received 4<sup>th</sup> October, 2019

Received in revised form 25<sup>th</sup>

November, 2019

Accepted 18<sup>th</sup> December, 2019

Published online 28<sup>th</sup> January, 2020

**Key words:**

Acute myeloid leukemia; Haploidentical transplant; Graft failure; Anti-HLA antibodies versus the donor.

### **ABSTRACT**

We describe the case of a 6 year old patient with high risk acute myeloid leukemia (AML), who received consolidation with a haploidentical paternal donor transplant with post-transplant cyclophosphamide to prevent graft versus host disease. Presents myeloid graft at day +14, chimerism of 90%, presenting graft failure at day +16. Secondary graft failure mediated by donor specific antibodies is diagnosed, desensitization is performed by immunoglobulin, rituximab and plasmapheresis therapy, and a 2nd. Transplant is performed, of the same donor, without success, raising the percentage of donor specific antibodies to 81% after the 2nd. Transplant. A new desensitization scheme is administered and ant thymocyte gamma globulin is added. Then, a 3rd. Haploidentical maternal donor transplant with post-transplant cyclophosphamide is performed. The patient has a successful myeloid graft on day +13 and pre-engraftment syndrome, as well as infection by BK virus consistent with prolonged deep neutropenia. Currently the patient is without infection, stable and conserving myeloid graft

Copyright© 2020 **Pamela Zazueta-Mérida et al.** This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

### **INTRODUCTION**

Se describe el caso de una paciente de 6 años de edad con leucemia mieloide aguda (LMA) de alto riesgo, la cual recibió consolidación con trasplante haploidentico de donador paterno con ciclofosfamida postrasplante para prevención de enfermedad injerto contra huésped. Presenta injerto mieloide al día +14, quimerismo del 90%, presentando falla de injerto al día +16. Se diagnostica falla de injerto secundaria mediada por anticuerpos específicos anti-HLA versus el donador, se realiza desensibilización mediante terapia con inmunoglobulina, rituximab y plasmaféresis, y se realiza 2da. Infusión del mismo donador sin tener éxito, elevando el porcentaje de anticuerpos anti-HLA hasta 81% tras el 2do. Trasplante. Se administra nuevo esquema de desensibilización y se agrega gammaglobulina anti-timocito. Se realiza 3er. trasplante haploidentico de donador materno con ciclofosfamida postrasplante. La paciente presenta injerto mieloide exitoso el día +13 y síndrome pre injerto, así como infección por virus BK consecuente a la neutropenia profunda prolongada,

actualmente la paciente se encuentra sin infección, estable y conservando injerto mieloide. **PALABRAS CLAVE:** Leucemia mieloide aguda; Trasplante haploidentico; Falla de injerto; Anticuerpos anti-HLA versus el donador.

### **Background**

Leukemia is the most common form of cancer in children (<15 years), accounting for almost one-third of all childhood leukemias. Acute myeloid leukemia (AML) contributes to 15-20% of the childhood leukemias. Prognosis for AML improved remarkably during the past decades, due to optimizing existing treatment strategies.<sup>1</sup> Allogenic hematopoietic cell transplantation (HCT) is the best curative treatment approach for a subset of children with refractory, relapsed, or molecularly determined high-risk disease. HCT is optimally successful at achieving long-term disease control when the leukemia burden at the time of transplant is minimal.<sup>2</sup>

Myeloablative-conditioning (MAC) regimens prior to allogenic transplantation is believed to control leukemia by combining intensive preparative therapy with the benefit of the graft vs. leukemia effect. Transplantation of grafts from an HLA-matched donor has generally been considered to be the

\*Corresponding author: **Pamela Zazueta-Mérida**

Department Of Prosthodontics, Crown and Bridge, Thai

Moogambigai Dental College and Hospital, Chennai- 600107

treatment of choice for children with AML in first complete remission.<sup>3</sup>

T-cell depleted hematopoietic stem-cell transplantation (HSCT) from an HLA-haploidentical relative is a feasible option for children needing an allograft and lacking an HLA-compatible donor. However, both primary (defined as lack of hematologic recovery or absence of donor chimerism) and secondary (defined as loss of donor chimerism after initial engraftment) graft failure, mainly mediated by host alloreactive T cells escaping the preparative regimen, have been reported in up to 15% to 18% of children given mismatched HSC transplants, despite de infusion of large numbers of hematopoietic stem cells. Recipients of T-Cell depleted HSC transplants from an HLA-disparate relative are also exposed to an increased risk of life-threatening infections, especially of viral origin, due to the delay in reconstitution of adaptive immunity.<sup>4</sup>

### **Clinical Case**

A 6 year-old Mexican female with a diagnosis of high-risk acute myeloid leukemia. Start induction treatment with ADE (Cytarabine 200mg/m<sup>2</sup>/day as a continuous IV infusion on days 1-4, Etoposide 100mg/m<sup>2</sup> on days 1-4 and Doxorubicin 75mg/m<sup>2</sup> on day 5) regimen, without achieving complete remission after the first cycle. Therefore, the induction scheme with HAM [Cytarabine 1000mg/m<sup>2</sup> as a 2 hour IV infusion every 12 hours day 1-3 (six doses), Mitoxantrone 10 mg/m<sup>2</sup> as a one hour IV infusion day 3-5, and Methotrexate intrathecal 12 mg. on day 1]5 regimen is modified, and after two cycles, the complete remission is achieved, with a minimum residual disease (MRD) report negative <1%. Consolidation phase begins with AML-BFM 04 protocol, to continue with treatment, prior to definitive consolidation with hematopoietic progenitors. After complete family assessment, the proposed model is a haploidentical paternal donor transplant, with cyclophosphamide post-transplant to prevent graft versus host disease.

As an important background, prior to transplantation, both donor and recipient presented positive for CMV IgG and both shared the same blood type A (+). However, the patient had a history of poly-transfusion, requesting upon admission a level of ferritin reported in 677 ng/ml and antibody reactive panel (PRA) reported positive in 14.3%, and Rituximab 345 mg/m<sup>2</sup> dose is indicated as desensitization prior to the onset of myeloablative conditioning. We decided to desensitize with a single dose of Rituximab, since the percentage of anti-HLA antibodies was not positive at more than 20%. Conditioning regimen is performed with Busulfan (1.1 mg/kg/day -7 to -4) and Cyclophosphamide (40mg/kg/day -3 and -2) without presenting adverse effects, performing a transplant on day 0, with CD34 dose 8.000x10<sup>6</sup>/kg and a CMN dose 3.41x10<sup>8</sup>/kg, without adverse effects during the infusion. Graft versus host disease prevention was performed on day +3 and +4, with Cyclophosphamide (50 mg/kg/day) and subsequently immunosuppression was started on day +5 with mycophenolate mofetil (15 mg/kg/dose) and tacrolimus (0.075 mg/kg/day), as well as stimulation of granulocyte colonies with Filgrastim (10 mcg/kg/day). Myeloid graft was documented on day +14, with an absolute neutrophil count of 790 m $\mu$ L, and 90% chimerism from the donor's DNA, however, graft is lost on day +16, categorized as secondary graft failure. After performing and analysis of the graft failure, it is found: negative viral infections, the dose of CD34 was

optimal, iron overload is ruled out, there is no history of extensive chemotherapy, myeloablative conditioning was considered adequate for the disease hematological, no graft disease against host after transplantation was documented, highlighting only the disparity of HLA between recipient and donor, requesting a new panel of anti-HLA antibodies reporting 2.6%, deciding to perform a 2nd. Infusion of the same donor.

The 2<sup>nd</sup>. Infusion was done with doses of CD34 8.00x10<sup>6</sup>/kg and CMN dose of 3.41x10<sup>8</sup>/kg, without presenting adverse effects. However, myeloid graft cannot be documented. Requesting a new panel of anti-HLA antibodies reporting 81%. Desensitization scheme is initiated by adding Methylprednisolone (2 mg/kg/day), Immunoglobulin for 3 doses (1 mg/kg) with weekly administration for 3 doses, Rituximab for two doses (345 mg/m<sup>2</sup>), two plasmapheresis sessions and ends with anti-thymocyte gamma-globulin (7 mg/kg) prior to 3rd. infusion. Due to the prolonged time of deep neutropenia of the patient, it is decided to make a donor change, proposing the same haploidentical transplant model but as a donor to the mother, with post-transplant cyclophosphamide. After the desensitization scheme, the 3rd. infusion is performed, with doses of CD34 8.000x10<sup>6</sup>/kg.

Subsequently, new panel of anti-HLA antibodies is requested of maternal donor, reporting 96%, so it continues with weekly dose of immunoglobulin (1 mg/kg). Similarly, prevention of graft versus host disease is initiated on day +3 and +4 with cyclophosphamide (50 mg/kg/day) and subsequently immunosuppression was started on day +5 with Mycophenolate Mofetil (15 mg/kg/dose) and Tacrolimus (0.075 mg/kg/day), as well as stimulation with Filgrastim (10 mcg/kg/day). Myeloid graft was documented on day +13, with an absolute neutrophil count of 620 m $\mu$ L, maintaining it for more than 3 days, accompanied by pre-graft syndrome with generalized maculo-papular rash in the extremities and thorax, chimerism is performed reporting 100%. After the presence of myeloid graft, the patient begins with dysuria and hematuria, diagnosing BK virus infection, which is currently under treatment. So far no data on graft versus acute host disease are documented, the patient is stable.

### **DISCUSSION**

Failure to engraft after hematopoietic stem cell transplantation (graft dysfunction) or to sustain engraftment (graft rejection) is a formidable complication due to many possible factors. These include inadequate stem cell numbers, infections, graft-versus-host disease and immunological mediated processes.

Failure to engraft after marrow ablative therapy is life-threatening but fortunately occurs at an overall frequency of less than 5%.<sup>6</sup> Engraftment after hematopoietic stem cell transplantation (HSCT), is defined as an absolute neutrophil count greater than 500 cells per liter [(ANC)>0.5x10<sup>9</sup>/L] on the first day of three consecutive days. Primary graft failure is characterized by the absence of initial donor cell engraftment (donor cells less than 95%); In contrast, secondary graft failure is characterized by loss of donor cells after initial engraftment and recurrent ANC < 0.5x10<sup>9</sup>/L.<sup>7</sup> It is a primary or secondary graft failure, it is essential to act as soon as the most serious consequence of the failure is the death of the patient.

Within the advantages of haploidentical transplantation Cyclophosphamide post-transplant (PT-Cy) is an attractive approach for crossing the HLA barrier in unmanipulated

Haplo-SCT because the treatment is cheap, strikingly effective, and requires no special expertise beyond chemotherapy administration. However, the complication of this model is the disparity in the HLAs and the consequent production of antibodies. The presence of DSA against the unshared haplotype in the recipient was associated with a 10-fold increased risk of engraftment failure.<sup>8</sup> Allo-sensitization towards major HLA antigens or, less frequently, minor histocompatibility antigens that develop as a consequence of previous blood product transfusions, can contribute to the increased rejection rate observed in nonmalignant diseases.<sup>9</sup>

The classical pathway of the complement cascade is activated when the antigen antibody complex binds to C1q and initiates activation of other complement components, resulting in the formation of membrane attack complex, which in turn causes cell lysis with apoptosis and clearance of the targeted cells. In HSCT, DSA that target donor HLA antigens present on the surface of hematopoietic progenitor cells, and antigen antibody complexes that may bind to C1q, activate the complement cascade and cause destruction of the donor cells, resulting in allograft rejection.<sup>10</sup> Nonetheless, consistently over the years, different groups suggested a pivotal pathogenic role of IFN $\gamma$  in GF pathophysiology, through both direct (e.g., inhibition of hematopoietic stem cell (HSC) self renewal, proliferative capacity, and multilineage differentiation) and indirect (e.g., induction of FAS expression on HSCs, with increased apoptosis in the presence of activated cytotoxic T cells) effects. IFN $\gamma$  is a potential therapeutic target in GF.<sup>11</sup>

A number of methods have been developed for the screening and specification of anti-HLA antibodies in transplant recipients. Generally, these methods are categorized into cell-based assays or solid-phase immunoassays. This method detects complement-activating antibodies lysing lymphocytes. The more sensitive method of antibody detection is flow cytometry crossmatch test. A positive test for DSA is considered when MFI is above 1,000; however, the cutoff of MFI values used varies among transplant centers and laboratories. Although rejection can occur at any DSA level for MFI > 1,000, the likelihood of developing PGF increases as the MFI levels increase. To reduce the risk of PGF, several desensitization methods have been used to decrease total antibody load to levels that would permit successful donor stem cell engraftment. These strategies to desensitize patients with DSA are classified into the following 4 strategies: (1) antibody removal by using plasmapheresis or immunoadsorption; (2) inhibition of antibody production by using monoclonal antibodies to CD20+ B lymphocytes (rituximab), and proteasome inhibitor against alloantibody producing plasma cells (bortezomib); (3) antibody neutralization using intravenous immunoglobulin (IVIg), or with donor HLA antigens (platelet transfusions or white blood cell infusion in the form of an irradiated "buffy coat"); and (4) inhibition of complement cascade. <sup>12</sup>

Because secondary myeloablative reconditioning regimens after graft failure in patients treated by allogeneic HCT are associated with unacceptable toxicity and subsequent mortality rates, a variety of different immunosuppressive approaches before re-transplantation have been developed. <sup>13</sup> Because of an increased risk of rejection and GVHD with repeated transplants, ATG or Campath may be considered during conditioning.<sup>14</sup>

## CONCLUSION

In our case, we considered that the initial PRA percentage was not high, so we only used one dose of Rituximab as desensitization. However, after the failure of the 2nd. Transplant, we decided to use other desensitization methods such as those mentioned above, since there is no standard. It is important to emphasize the high risk of morbidity and mortality associated with deep pancytopenia, so we decided to modify the donor to shorten this window, which in the end caused us infection with BK virus after the 3rd. transplant, without causing mortality. At present, haploidentical transplantation is considered a successful model, especially in candidates who do not have a compatible HLA donor, however, we consider it important to expose all the risks and potential complications. In our case, we propose, the use of a protocol based on treatment with plasmapheresis and Rituximab, since it is an adequate strategy to avoid of control the mechanism mediated by anti-HLA antibodies, and the use of gamma-globulin can increase the efficacy as in this case.

## References

1. Reedijk A, Klein K, Coebergh J, Kremer L, Dinmohamed A, de Haas V *et al.* Improved survival for children and young adolescents with acute myeloid leukemia: a Dutch study on incidence, survival and mortality. 2019.
2. Kussman A, Shyr D, Hale G, Oshrine B, Petrovic A. Allogeneic hematopoietic cell transplantation in chemotherapy-induced aplasia in children with high-risk acute myeloid leukemia or myelodysplasia. 27th ed. Pediatric Blood & Cancer. Saint Petersburg: Wileyonlinelibrary; 2018. p. 1 a 3.
3. Bitan M, He W, Zhang M, Abdel-Azim H, Ayas M, Bielgorai B *et al.* Transplantation for children with acute myeloid leukemia: a comparison of outcomes with reduced intensity and myeloablative regimens. 2019.
4. Ball L, Bernardo M, Roelofs H, Lankester A, Cometa A, Egeler R *et al.* Cotransplantation of ex vivo-expanded mesenchymal stem cells accelerates lymphocyte recovery and may reduce the risk of graft failure in haploidentical hematopoietic stem-cell transplantation. 1st ed. Bloodjournal. Washington DC 20036: Blood; 2007. p. 2764-2767.
5. Abrahamsson J, GötalandRegionen V, Hasle H. NOPHO-DBH AML 2012 Protocol [Internet]. Skion.nl. 2013 Available from: [https://www.skion.nl/workspace/uploads/NOPHO-DBH-AML-2012-Protocol\\_v2-1\\_17012013.pdf](https://www.skion.nl/workspace/uploads/NOPHO-DBH-AML-2012-Protocol_v2-1_17012013.pdf)
6. Wolff S. Second hematopoietic stem cell transplantation for the treatment of graft failure, graft rejection or relapse after allogeneic transplantation. [www.nature.com/bmt](http://www.nature.com/bmt). 2002.
7. Ozdemir Z, CivrizBozdağ S. Graft failure after allogeneic hematopoietic stem cell transplantation. [www.elsevier.com/locate/transci](http://www.elsevier.com/locate/transci). 2018.
8. Bramanti S, Calafiore V, Longhi E, Mariotti J, Crespiatico L, Sarina B *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. <https://doi.org/10.1016/j.bbmt.2019.02.020>. 2019.

9. Locatelli F *et al.* Current and future approaches to treat graft failure after allogeneic hematopoietic stem cell transplantation. - PubMed - NCBI. Ncbi.nlm.nih.gov. 2014
10. Ciurea S, Thall P, Milton D, Barnes T, Kongtim P, Carmazzi Y *et al.* Complement-Binding Donor-Specific Anti-HLA Antibodies and Risk of Primary Graft Failure in Hematopoietic Stem Cell Transplantation. journal homepage: www.bbmt.org. 2015.
11. Merli P, Caruana I, De Vito R, Strocchio L, Weber G, Del Bufalo F *et al.* Role of IFN $\gamma$  in immune-mediated graft failure occurring after allogeneic hematopoietic stem cell transplantation. *haematol.* 2019.
12. Ciurea S, Cao K, Fernandez-Vina M, Kongtim P, Malki M, Fuchs E *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 [Internet]. *Bone Marrow Transplantation - Review Article.* 2017. Available from: <https://doi.org/10.1038/s41409-017-0062-8>.
13. Wegener D, Lang P, Paulsen F, Weidner N, Zips D, Ebinger M *et al.* Immunosuppressive Total Nodal Irradiation-Based Reconditioning Regimens After Graft Rejection or Graft Failure in Pediatric Patients Treated With Myeloablative Allogeneic Hematopoietic Cell Transplantation [Internet]. *www.redjournal.org.* 2018 Available from: <https://doi.org/10.1016/j.ijrobp.2018.12.031>.
14. Mattsson J, Ringdén O, Storb R. Graft Failure after Allogeneic Hematopoietic Cell Transplantation [Internet]. *American Society for Blood and Marrow Transplantation.* 2008. Available from: <http://doi:10.1016/j.bbmt.2007.10.025>

**How to cite this article:**

Pamela Zazueta-Mérida *et al* (2020) 'Haploidentical Transplantation Injury Failure in A Girl with Acute Myeloid Leukemia', *International Journal of Current Advanced Research*, 09(01), pp. 20917-20920.  
DOI: <http://dx.doi.org/10.24327/ijcar.2020.4098.20920>

\*\*\*\*\*