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Case Report

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Successful Allogeneic Hematopoietic Stem Cell Transplantation From A 5/10 Mismatched Unrelated Donor In A Patient With Donor-Specific Anti-HLA Antibodies.

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Abstract

Hematopoietic stem cell transplantation (HSCT) from a mismatched unrelated donor, an haploidentical donor or a cord blood unit (CBU) has become a widely aviable approach if patient lacks a matched related or unrelated donor.

However, if the patient has anti-HLA antibodies against antigens present in the mismatched donor or CBU (donor-specific antibodies, DSAs) this option should be disregarded due to the high risk of graft failure.

Desensitization can be used to reduce levels of DSAs but this technique has limited results.

We report the case of a 62-year-old woman with DSAs against two haploidentical familiar donors who failed desensitization of DSAs. Finally she underwent a HSCT from a 5/10 mismatched unrelated donor which has been successful.

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Introduction

Currently, for patients requiring hematopoietic stem cell transplantation (HSCT) but lacking a matched related or a matched unrelated donor (MUD) (20%) an HSTC from a mismatched unrelated donor (mMUD), a cord blood unit (CBU) or an HLA-haploidentical HSCT (haplo-HSCT) represent a widely available approach.

Several studies show that high dose cyclophosphamide administered after HCT (PTCy) is a feasible option for haploidentical and mismatched in terms of safety profile and low rates of graft versus host disease (GVHD) and transplant non-related mortality (NRM) [1,2]

HLA antibodies should be examined as part of the pre-transplant work-up, especially in transplants with HLA-mismatches planned for parous women and multi-transfused receptors. Furthermore, donors who have HLA antigens that correspond to high levels of donor-specific anti-HLA antibodies (DSAs) in the patient should be avoided. DSAs are considered positive when median fluorescence intensity (MFI) is > 3000 -5000 and > 10.000 as very high levels corresponding to the mismatched donor HLA antigen[3,4]

Thus, if the patient has donor-specific anti-HLA antibodies against antigens present in the mismatched donor or CBU, this option should be disregarded due to the high risk of graft failure (GF)[3,5, 6,] .

The risk of GF in the presence of DSAs is approximately 70% after T-cell replete and T-cell deplete haplo-HSCT and after CBU transplants. Similarly, after mMUD transplant the risk is between 11 to 22% [3,5,6,7]

In an attempt to reduce DSAs, desensitization can be used but if levels of DSAs are high, this technique has limited results [4,3,8]

Case Description

A 62 year-old woman with a high-risk acute myeloid leukemia (high ratio FLT-ITD mutation and NPM1 mutation) was diagnosed on December 2016. The patient weighed 58 Kg and had a history of one pregnancy. After induction chemotherapy that included idarubicin, cytarabine and midostaurine, she achieved a complete response. She then received three consolidation cycles with high dose cytarabine.

Because of the poor prognosis and high risk of relapse[8,9] an allogeneic HCT was planned. The patient had no HLA identical sibling nor 9/10-10/10 unrelated donor. A search for CBU was also performed but all units were discharged because of low cellularity. Two familiar haploidentical donors (sister and son) were identified but the patient had high titters of DSAs (16616 MFI against B*49:01, 18464 MFI against DQB*03:01/DQ DRB1*11:01, and 20810 MFI against DRB1*11:01). Before the transplant, during the aplasia after chemotherapy, she had received transfusions with 19 RBC units and 29 pools of platelets.

At this stage, a desensitization treatment including plasma exchange, rituximab and immunoglobulins as a new treatment strategy for severe HLA alloimmune platelet refractoriness[11] was administered without success.

For this reason, a directed search for mMUD for which the patient did not have DSAs, was performed through the Spanish Marrow Donor Registry (REDMO).

A 30 year-old-female donor weighing 68 Kg, with intermediate CMV risk (patient + /donor +) and major bidirectional ABO incompatibility (patient A +/ donor B +) was found. Between donor and patient there were 5 out of 10 HLA-mismatches, 3 at antigen level (loci A, C, and DRB1) and 2 at allele level (loci B and DQ).

In Table 1 appear the HLA genotype of the patient and the donor.

Although the patient was extensively alloimmunized, she had no DSAs against the donor mismatches.

The patient received our standard conditioning regimen for haploidentical transplantation for patients older than 50 years, with fludarabine 30 mg/sqm (days -6 to -2) and busulfan 3.2 mg/sqm (days -7 to -5) and 2Gy TBI (day -1), followed by the infusion of 8 x 10^6 CD34+/kg, 603·106 /CD3+/kg on day 0 (12/05/2017). She did not receive stimulants of the granulocyte colonies (GCSF).

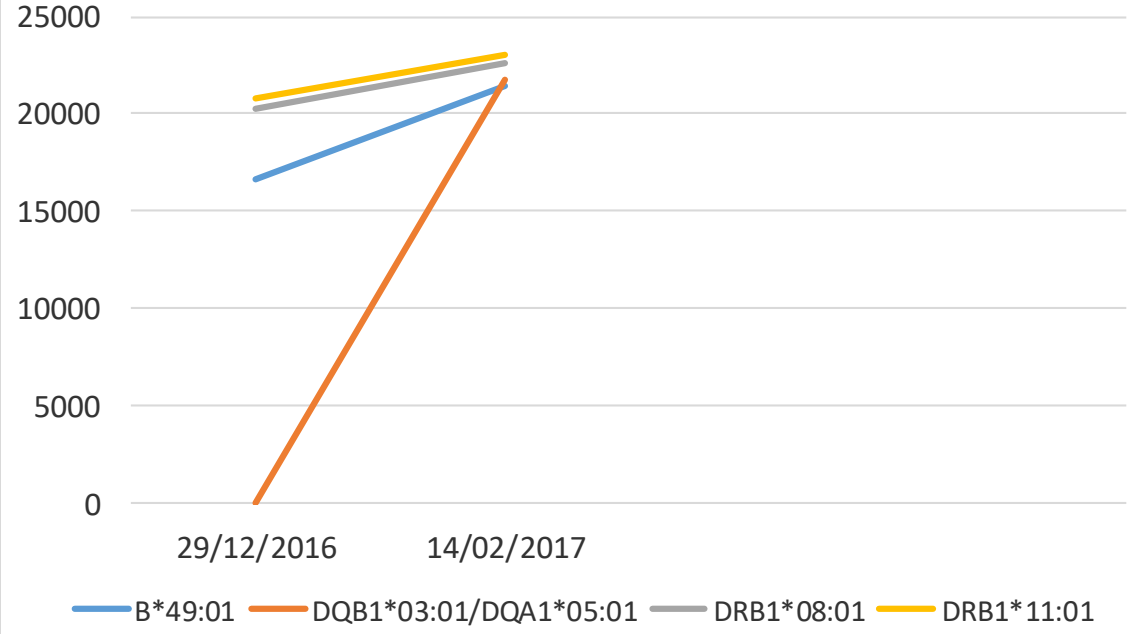
A panel of selected platelet donors where identified before transplantation to ensure adequate platelet transfusions during aplasia. The patient did not present any bleeding problems.

GVHD prophylaxis was done with high dose PTCy (+3

Table 1. HLA PATIENT/DONOR

HLA PATIENT									
A*24:02 P	A*29:02 P	B*14:02 P	B*38:01 P	C*02:02 P	C*12:03 P	DRB1*01:01P	DRB1*04:04P	DQB1*05:01P	DQB1*03:02P
HLA DONOR									
A*32:01 P	A*29:02 P	B*14:01 P	B*38:01 P	C*08:02 P	C*12:03 P	DRB1*01:01P	DRB1*10:01P	DQB1*05:01:01	DQB1*-

Table 2. DSAs against HLA antigens of sister and son pre and after desesitization



and +4), tacrolimus and mycophenolate. The patient achieved neutrophils ≥500/μL on day +23 and platelets ≥20.000/μL on day +25. At + 30, full donor chimerism on neutrophils and T lymphocytes was achieved.

There were no severe complications except a grade IV mucositis, cervical edema without any radiological findings that was resolved with antibiotic and antifungal therapy, a CMV reactivation that was treated with valganciclovir and a biological TMA at +35 which was resolved by withdrawing tacrolimus and adding rapamycin.

After 9 months, the patient continues in CR, with full donor chimerism, and no GVHD has occurred.

Conclusions

This is a successful HLA- 5/10 mMUD-HSCT in a woman that without this strategy wouldn´t have been transplanted. Taking into account the list of the DSAs, REDMO did a manual selection of the possible donors, selecting those that for which the patient didn´t have DSAs.

With the classical conditioning and GVHD proplylaxis with PTCy used in the haploidentical transplants, the patient engrafted, faster full chimerism was achieved and she didn´t present GVHD.

This case highlights that almost every patient that needs an allogeneic transplantation can have a donor. In such difficult cases of patients who lack of HLA matched related or unrelated donors, and who have DSAs that rules out the possibility of an haploidentical related or a mismatched unrelated transplantation, an individualized strategy together with the registry should be taken to select mMUD to which a patient has no DSAs.

Aknowledgements

Autorship

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References

1. Kasamon, Y., Ambinder, R., Fuchs, E., Zahurak, M., Rosner, G., Bolaños-Meade, J., Levis, M., Gladstone, D., Huff, C., Swinnen, L., Matsui, W., Borrello, I., Brodsky, R., Jones, R. and Luznik, L. (2017). Prospective study of nonmyeloablative, HLA-mismatched unrelated BMT with high-dose posttransplantation cyclophosphamide. Blood Advances, 1(4), pp.288-292.
2. Kanakry, C., Bolaños-Meade, J., Kasamon, Y., Zahurak, M., Durakovic, N., Furlong, T., Mielcarek, M., Medeot, M., Gojo, I., Smith, B., Kanakry, J., Borrello, I., Brodsky, R., Gladstone, D., Huff, C., Matsui, W., Swinnen, L., Cooke, K., Ambinder, R., Fuchs, E., de Lima, M., Andersson, B., Varadhan, R., O'Donnell, P., Jones, R. and Luznik, L. (2017). Low immunosuppressive burden after HLA-matched related or unrelated BMT using posttransplantation cyclophosphamide. Blood, 129(10), pp.1389-1393.
3. oshihara, S., Taniguchi, K., Ogawa, H. and Saji, H. (2012). The role of HLA antibodies in allogeneic SCT: is the 'type-and-screen' strategy necessary not only for blood type but also for HLA?. Bone Marrow Transplantation, 47(12), pp.1499-1506.
4. Gladstone, D., Zachary, A., Fuchs, E., Luznik, L., Kasamon, Y., King, K., Brodsky, R., Jones, R. and Leffell, M. (2013). Partially Mismatched Transplantation and Human Leukocyte Antigen Donor-Specific Antibodies. Biology of Blood and Marrow Transplantation, 19(4), pp.647-652.
5. Ciurea, S., de Lima, M., Cano, P., Korbling, M., Giralt, S., Shpall, E., Wang, X., Thall, P., Champlin, R. and Fernandez-Vina, M. (2009). High Risk of Graft Failure in Patients With Anti-HLA Antibodies Undergoing Haploidentical Stem-Cell Transplantation. Transplantation, 88(8), pp.1019-1024.
6. Spellman, S., Bray, R., Rosen-Bronson, S., Haagenson, M., Klein, J., Flesch, S., Vierra-Green, C. and Anasetti, C. (2010). The detection of donor-directed, HLA-specific alloantibodies in recipients of unrelated hematopoietic cell transplantation is predictive of graft failure. Blood, 115(13), pp.2704-2708.
7. Taylor, P., Ehrhardt, M., Roforth, M., Swedin, J., Panoskaltsis-Mortari, A., Serody, J. and Blazar, B. (2006). Preformed antibody, not primed T cells, is the initial and major barrier to bone marrow engraftment in allosensitized recipients. Blood, 109 (3), pp.1307-1315.

8. Bramanti, S., Nocco, A., Mauro, E., Milone, G., Morabito, L., Sarina, B., Crocchiolo, R., Timofeeva, I., Capizzuto, R., Carlo-Stella, C., Santoro, A. and Castagna, L. (2016). Desensitization with plasma exchange in a patient with human leukocyte antigen donor-specific antibodies before T-cell-replete haploidentical transplantation. Transfusion, 56(5), pp.1096-1100.
9. Pratcorona, M., Brunet, S., Nomdedeu, J., Ribera, J., Tormo, M., Duarte, R., Escoda, L., Guardia, R., Queipo de Llano, M., Salamero, O., Bargay, J., Pedro, C., Marti, J., Torrebadell, M., Diaz-Beya, M., Camos, M., Colomer, D., Hoyos, M., Sierra, J. and Esteve, J. (2013). Favorable outcome of patients with acute myeloid leukemia harboring a low-allelic burden FLT3-ITD mutation and concomitant NPM1 mutation: relevance to post-remission therapy. Blood, 121(14), pp.2734-2738.
10. Schnittger, S., Bacher, U., Kern, W., Alpermann, T., Haferlach, C. and Haferlach, T. (2011). Prognostic impact of FLT3-ITD load in NPM1 mutated acute myeloid leukemia. Leukemia, 25(8), pp.1297-1304.
11. Cid, J., Magnano, L., Acosta, M., Alba, C., Esteve, J. and Lozano, M. (2014). Rituximab, plasma exchange and intravenous immunoglobulins as a new treatment strategy for severe HLA alloimmune platelet refractoriness. Platelets, 26(2), pp.190-194.