DESENSITIZATION FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION: CASE REPORT

Dessensiblização no transplante de células-tronco hematopoéticas: relato de caso

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ABSTRACT

Purpose: The presence of anti-human leukocyte antigen (HLA) antibodies has been correlated with graft failure in organ and tissue transplantation, demonstrating the importance of screening for antibodies before transplant. The purpose of the study is to report the desensitization protocol used for pre-transplant treatment of hematopoietic stem cells (HSCT) in previously sensitized patients. **Methods**: Case report of two cases of patient with high HLA specific antibody titers submitted to a desensitization protocol for allogeneic HSCT at a reference center for HSCT in Southern Brazil. The desensitization protocol consisted of rituximab and plasma exchange (PLEX) three times a week, with human immunoglobulin replacement (IVIg) after each session. **Results**: The first patient had a panel-reactive antibodies class I (PRA-I) score of 97%, with 20 highly reactive antibodies and no detectable DSA. The decision was made to attempt antibody desensitization to facilitate platelet transfusion during HSCT, which was completed after nine sessions of plasma exchange (PLEX), resulting in a reduction in PRA-I of 71%, and no highly reactive antibodies were detected. The second patient presented a PRA-I score of 53% and PRA class II (PRA-II) of 99%, including 16 highly reactive antibodies and DSA against both possible donors. After the ninth session of PLEX, treatment was intensified and continued until the end of the 19 sessions. At the end of the protocol, PRA-I and PRA-II had been reduced to 0% and 87% respectively, with persistent presence of only two highly reactive antibodies and no detectable DSA. **Conclusion**: The antibody desensitization and select platelet donor transfusion assured a more appropriate transfusion support to a HLA sensitized patient refractory to platelet transfusion with a matched sibling donor and PRA monitoring being essential for defining the appropriate desensitization regimen to a patient with DSAs and haploidentical donor.

Keywords: Hematopoietic Stem Cell Transplantation; Desensitization, Immunologic; HLA Antigens; Plasmapheresis.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for several diseases. Advances made in this field are attributable to improvements in the HLA (human leukocyte antigen) typing; more stringent donor selection; advanced conditioning regimens, especially reduced-intensity; and diligent supportive care, particularly during the aplastic phase.[1,2]

In allogeneic HSCT, HLA compatibility plays a key role in the transplantation process, and is directly associated with several post-HSCT complications and patient survival. Improvements in immunohematology and the use of more advanced testing techniques have resulted

in better donor selections, and have made possible the use of hematopoietic stem cell sources, despite the HLA incompatibility. However, the presence of HLA-specific antibodies, especially HLA-specific antibodies against the donor (DSA) can pose a particularly challenging barrier in the treatment of these patients. The HLA-specific antibodies can be developed after exposure to non-selfcells, triggering an immune response. The main risk factors of sensitization to HLA antigens are a history of multiple blood and platelet transfusions, previous transplant, and pregnancy.[3]

The degree of sensitization will vary according to the amount of antibodies produced.[4] A panel reactive antibody (PRA) test can demonstrate which anti-HLA antibodies are present in the serum of a patient, assessing these antibodies in a semiquantitative manner and classifying them according to their mean fluorescence intensity (MFI). The presence of DSAs in PRA was correlated to a primary graft failure, relapse, reduced disease-free survival and overall survival, even at low rates.[3] However, the association between the presence of non-DSA antibodies in the recipient or HLA antibodies development in the post-transplantation phase with negative transplant outcomes is less explored, with few studies showing an association between these antibodies and worse rate survival.[5,6]

Therefore, it is recommended that pre-transplant PRA screening be performed in which prospective donors are HLA-incompatible, especially in candidates for haploidentical HSCT, and considered in patients with other immunological risk factors or conditions which can have a negative impact in the transplant outcome, as platelet transfusion refractoriness (PTR).[5,6] Recent advances in the adaptation of desensitization protocols, mainly in renal transplants have allowed for HSCT to be performed in a greater number of sensitized individuals, with satisfactory results.[3] In that context, this brief report describes the use of a desensitization protocol in two sensitized stem cell transplant patients.

MATERIAL AND METHODS

Case report of two patients who completed pre-HSCT desensitization protocols at a reference center for HSCT in Southern Brazil. The desensitization protocol was carried out as reported by Montgomery et al. (2011),[7] in Prisma® systems by using plasma filters.

The study was approved by the Institutional Review Board (IRB No. CAAE 02898218.0.0000.5330, opinion number 3.934.849). Patients undergoing HSCT agreed to participate in this study and provided written informed consent. Data were collected on the electronic medical records of patients.

Antibody determination was set by using a Luminex® single-antigen bead solid-phase assay (One Lambda, USA). Sera were heat-treated before testing in order to prevent false negatives. In this study, the MFI parameter was used to quantify antibodies according to the following classification scheme: low reactivity (1000 to 2000), medium reactivity (2001 to 5000), and high reactivity (>5000). Cross-matching was performed by flow cytometry, following the Halifax protocol.[8]

RESULTS

Case 1

An 18-year-old female diagnosed with hypoplastic anemia in 2012 and myelodysplastic syndrome in 2015, refractory to thymoglobulin and cyclosporine treatment was referred for a HLA-identical sibling HSCT. Given the long-term history of recurrent blood transfusions and persistently platelets count below 5.000 mm³ despite transfusions of the patient, a pre-HSCT PRA screening was performed. The panel showed 97% reactivity to PRA class I (PRA-I) with pure serum, 92% with a 1:10 dilution, and 88% with 1:20 dilution. Overall, 37 anti-HLA class I antibodies were detected, from which 20 were highly reactive. No DSAs were detected, and crossmatch testing with the donor (the sister of the patient) was negative. Although PRA measured disclosed no DSA, and the decision was made to attempt antibody desensitization in order to facilitate platelet transfusion during HSCT. Besides that, platelet donors were screened by using virtual and in vitro crossmatch tests in order to improve the platelet transfusion increment and avoid additional HLA alloimmunization, and only three compatible donors were available at the time of the assessment.

The desensitization protocol consisted of rituximab 375 mg/m² and one plasma volemia exchange three times a week, followed by a 4% human intravenous immunoglobulin (IVIg) replacement (0.1 mg/kg).

No complications were reported during plasma exchange (PLEX) sessions. However, elevated platelet consumption was identified, with a decline in the platelet count from 40,000 to 24,000 after the first session and from 19,000 to 8,000 after the second session. After the second PLEX session, the system anticoagulant was switched from heparin to sodium citrate for the remainder of the treatment, and platelet consumption decreased to expected levels. After six PLEX sessions, the PRA-I score had been reduced to 74% with 1:10 serum dilution and 0% with the 1:20 dilution, and all highly reactive anti-HLA antibodies had become undetectable.

PLEX sessions were continued until conditioning in order to avoid rebound production of anti-HLA antibodies. The patient's conditioning regimen included busulfan (12.8 mg/kg from D-7 to D-4), cyclophosphamide (120 mg/kg from D-2 to D-1) and antithymocyte globulin (10 mg/kg from D-4 to D-1). The graft-versus-host disease (GVHD) prophylaxis was methotrexate, cyclosporine and mycophenolate mofetil. However, the patient developed life threatening anaphylaxis associated to ATG, requiring intensive care and delaying conditioning and subsequently postponing the graft infusion date by two days. In addition, the patient was diagnosed with fungal pneumonia, and an amphotericin B lipid complex treatment was initiated. The patient received 8.9×10^6 CD34+ donor cells/kg, with no infusion-related complications. Control PRA could not be performed before the graft infusion due to logistical issues. When eventually performed 3 days after HSCT, it showed a rebound compared to values obtained during the desensitization protocol, with a PRA-I score of 89% with six highly reactive anti-HLA antibodies. Nevertheless, the patient showed improvement in platelet increment during pancytopenia, and the engraftment happened 17 days post bone marrow infusion. PRA testing was repeated showing a reduction of 72% in the PRA-I score, without any highly reactive anti-HLA antibodies at that time. The patient was diagnosed with cytomegalovirus reactivation and treated with ganciclovir having a good initial response. However, the patient developed progressively worsening respiratory failure and as a result, an invasive diagnostic workup could not be performed due to severe thrombocytopenia. Repeat PRA testing showed a minor increase in the PRA-I score reaching 76%. Despite a change in the reactivity of anti-HLA antibodies, no new antibodies were identified when compared to the first assay administered.

Due to persistent worsening of respiratory function, most likely due to an inflammatory reaction of lung tissue to antifungal therapy and white blood cell recovery, treatment with methylprednisolone 2 mg/kg and general intensive care measures were implemented. As a result, an improvement in pulmonary condition was observed and the patient was discharged from the intensive care unit (ICU). Nevertheless, 40 days following the HSCT, the patient presented a progressive rash, vomiting, diarrhea, anorexia and, ultimately, septic shock. Gastrointestinal (GI) tissue biopsies were consistent with grade IV acute GVHD, which was refractory to corticosteroids and immunotherapy and the patient did not survive.

Case 2

A 38-year-old woman diagnosed with acute myelomonocytic leukemia (M4) treated with cytarabine (100 mg/m²/ day IV on D1-D7), idarubicin (12 mg/m²/ day IV on D1-D3) and 4 cycles of cytarabine (3 g/m² IV q12h on D1-D3) with complete remission. The patient was referred for a haploidentical HSCT with two suitable options of sibling donors (dizygotic twins). PRA-I and PRA-II panels showed 53% and 99% reactivity, respectively, with 16 highly reactive anti-HLA class II antibodies. The patient was positive for DSA to donor 1 (anti-A11, low reactivity; anti-DQ2, high reactivity; anti-DR13, low reactivity) and donor 2 (anti-DR11, high reactivity; anti-DR13, low reactivity). Due to the high PRA scores (especially class II) and detection of DSA to both donors, the desensitization protocol was started with rituximab (375 mg/m²), one plasma volemia exchange three times a week, and 4% IVIg replacement (0.1 mg/kg/session). Sodium citrate was used for system anticoagulation;which caused a decline in fibrinogen, managed with close monitoring of coagulation and cryoprecipitate infusion as needed. After five days of rituximab infusion and immediately before the start of PLEX, a new PRA-II panel showed a short score reduction to 95% and the presence of 11 highly reactive antibodies; all DSAs persisted at the same levels of reactivity, except for anti-DQ2 DSA against donor 1, which was not detected. PRA was repeated between the fourth and fifth PLEX sessions and showed only minimal response, with PRA-II score unchanged at 95% and persistent presence of 12 highly reactive anti-HLA antibodies. Anti-DQ2 DSA to donor 1 showed high reactivity, whereas anti-DR11 DSA to donor 2 showed medium reactivity, however, the anti-DR13, previously identified against both donors, was no longer detected.

Given this unsatisfactory result, the desensitization protocol was intensified after the eighth PLEX session. A second dose of rituximab was infused (375 mg/m²), the PLEX was increased to one and a half volemia, and the IVIg replacement dose was doubled (0.2 mg/kg/session). Before intensification of the protocol, a new PRA-II panel was run which showed a score of 95% and 12 highly reactive antibodies. This panel detected two DSAs: anti-DQ2 to donor 1 with high reactivity and anti-DR11 to donor 2 with medium reactivity.

Before the 14th session (i.e., the sixth session of intensified desensitization), the PRA-I and PRA-II scores were 15% and 93% respectively, with 9 high reactive antibodies and detection of one DSA (anti-DQ2, donor 1) with medium reactivity. After the 14th session, the panel showed a 0% score for class I and 80% for class II antibodies and a single highly reactive antibody, with no detectable DSA to either of the potential donors. After the 15th session, the panel showed 0% reactivity for class I (same as previous session) and 87% reactivity for class II, with two highly reactive antibodies (both

class II); no detectable DSA was found in either potential donor. Crossmatching of both potential donors was performed, showing a positive result for B lymphocytes. Both donors were equally suitable, however donor 1 was chosen because of the availability. The patient conditioning regimen included busulfan (440 mg/m² from D-7 to D-4); fludarabine (125 mg/m² from D-6 to D-2); and cyclophosphamide (29 mg/kg from D-3 to D-2). The GVHD prophylaxis was cyclophosphamide, tacrolimus and mycophenolate mofetil. The PLEX regimen continued until the day before the graft infusion, and desensitization was completed after 18 sessions (10 sessions with the intensified protocol). The patient received 10.44x10⁶ CD34+ cells/kg of peripheral HSCs, with no infusion-related complications.

During the aplastic phase, the patient had a febrile neutropenia of unknown origin, with no major complications. Engraftment was detected 15 post-infusion days. At the time, acute GVHD in the GI tract was suspected due to abdominal pain and liquid stool episodes; methylprednisolone 2 mg/kg/day was started with a satisfactory response. A CMV reactivation was diagnosed with good response upon ganciclovir treatment. The patient also developed hematuria and dysuria, and a high BK polyomavirus load was detected in the urine. Once viral reactivation was resolved, the patient was discharged. Currently, the patient is in the long term outpatient follow-up, with no GVHD activity, in complete remission 2 years post-HSCT.

DISCUSSION

HLA screening prior to HSCT has been widely used since the 1960s in order to select the most appropriate donor. Advances in high-resolution HLA detection techniques and in the analysis of PRAs to HLA mismatched, whether related or not to transplants have significantly improved donor selection, pre-transplant desensitization protocols design and transplant outcomes.[9]

The single-antigen bead assay is used to detect and perform semi quantitatively assessment of antibodies against HLA class I and class II system antigens, and the crossmatch is a technique used to assess the in vitro presence of preformed antibodies in the blood of the recipient against cells of the possible donor.

In case 2, PRA was essential to follow the DSA curve of both potential donors, and thus to assist in the donor selection. A positive crossmatch testing are now known to be associated with a high incidence of graft failure, early relapse, and reduced overall disease-free survival, highlighting the importance of conducting pre-transplant antibody screening to the donor selection and deciding on the optimal HSCT type in patients with risk factors.[3,5,10-13]

In case 1, PRA was performed to follow the reduction in the amount and reactivity of the anti-HLA class I antibodies, in order to improve platelet transfusion increment during the aplasia phase in a patient with severe PTR. HSCT patients often demonstrate poor increments to platelet transfusions due to pre-existing HLA alloimmunization, medications, viral infections and sepsis with an increased risk for severe hemorrhage.[1] HLA class I (HLA-A and -B antigens) alloimmunization is the primary cause of immune-mediated PTR,[14] with rates ranging from 7 to 55% after platelet transfusion,[15-17] while alloantibodies against human platelet antigens (HPA) are responsible by only 0–2% of the cases.[18,19] The high frequency rate of alloimmunization related to higher blood transfusion requirement in patients with hematologic disease as hypocellular myelodysplasia syndrome and aplastic anemia emphasizes the importance of the HPA and PRA screening.[20,21] A negative crossmatch testing between recipient and platelet from donors is known to provide good corrected count increment for alloimmunized PTR patients.[22]

The desensitization protocol with plasma exchange, rituximab and IVIg known to induce an adequate reduction in DSA, has been widely used in solid organ transplantation and is currently being used as pre-HSCT regimen in sensitized patients.[23-27] In the two cases described, given the high antibody titers detected, one with DSA and the other with severe immune platelet refractoriness, a therapeutic regimen of rituximab and PLEX with IVIg was administered.

PRA follow-up is essential for monitoring the results of the desensitization protocol and for the early identification of possible rebound effects, which may occur due to pro-inflammatory events and infections during the conditioning period.[28] In both cases, PRA monitoring allowed the assessment of the response of patients to the selected protocol. In case 2, the protocol was intensified after the sixth session due to a response not consistent with our expectations. The changes included an increase in the processed blood volume and IVIg dose, as well as the application of a second dose of rituximab. Some protocols define intensity according to the patient's degree of sensitization and response.[29]

Several clinical scenarios can also interfere with the desensitization. There are reports that pregnancy-induced sensitization can result not only in humoral but also in cellular sensitization, with impacts on the outcome, depending on the selected protocol.[29]

PRA monitoring in the post-HSCT period also enables early identification of rebound events, allowing a more effective intervention. In the case of patient 1, there was an increase in the PRA after HSCT, probably due to an anaphylactic shock after the administration of antithymocyte globulin during the conditioning or to the pulmonary fungal infection identified after transplantation. After this event, the PRA values remained stable, and additional measurements were deemed unnecessary. Some protocols predict PRA monitoring in the first week after HSCT on days D+3, D+5 and/or D+7 or as needed. [29]

The detection of DSA before HSCT is associated with increased disease relapse rates and reduced overall survival.[11-13] However, due to our small sample size, we were unable to make any comparisons in this respect. Further studies are needed to define the impact of DSA on HSCT outcomes and its complications.

CONCLUSION

Analysis of anti-HLA antibodies has become an essential factor in the selection and follow-up of desensitization protocols, allowing a risk reduction of transplant-related complications. Nowadays, transplant centers have seen an increase in the amount of sensitized patients who are candidates for HSCT due to several reasons, including: an increasing amount of HLA-mismatched transplants; inadequate transfusion support and longer waiting times for transplantation. Therefore, the transplant teams must assess the presence of risk factors of patients for sensitization and the possible need for a desensitization pre-transplant.

RESUMO

Objetivo: A presença de anticorpos anti-HLA (antígeno leucocitário humano) tem sido correlacionada com a falha do enxerto de órgãos e tecidos transplantados, demonstrando a importância da triagem desses anticorpos antes do transplante. O objetivo do estudo é relatar o protocolo de dessensibilização utilizado para tratamento pré-transplante de células-tronco hematopoéticas (TCTH) em pacientes previamente sensibilizados. **Métodos**: Relato de caso de dois pacientes com altos títulos de anticorpos específicos ao antígeno leucocitário humano (HLA) submetidos a um protocolo de dessensibilização para TCTH alogênico em um centro de referência no sul do Brasil. O protocolo de dessensibilização utilizou rituximabe e plasmaférese (PLEX), três vezes por semana, com reposição de imunoglobulina humana (IVIg), após cada sessão. **Resultados**: O primeiro paciente apresentou painel de reatividade contra anticorpos classe I (PRA-I) de 97%, com 20 anticorpos altamente reativos e DSA indetectável. A decisão pela realização da dessensibilização foi para facilitar a transfusão de plaquetas durante o TCTH. O protocolo foi concluído após nove sessões de plasmaférese (PLEX), resultando em uma redução no PRA-I de 71%, sem detecção de nenhum anticorpo altamente reativo. O segundo paciente apresentou escore PRA-I de 53% e PRA classe II (PRA-II) de 99%, incluindo 16 anticorpos altamente reativos e DSA contra os dois possíveis doadores. Após a nona sessão de PLEX, o tratamento foi intensificado até o final das 19 sessões. Ao final do protocolo, PRA-I e PRA-II foram reduzidos para 0% e 87%, respectivamente, com presença persistente de apenas dois anticorpos altamente reativos e nenhum DSA detectável. **Conclusão**: A dessensibilização e a transfusão de plaquetas com doador selecionado garantiram um suporte de transfusional mais adequado em um paciente com doador HLA idêntico e refratariedade à transfusão de plaquetas por anticorpos HLA, e o monitoramento de PRA e a triagem de DSA foram essenciais para definir o regime de dessensibilização apropriado em um paciente com DSAs e doador haploidêntico, reduzindo assim os riscos do TCTH.

Descritores: Transplante de Células-Tronco Hematopoéticas; Dessensibilização Imunológica; Antígenos HLA; Plasmaferese.

REFERÊNCIAS

1. Gyurkocza B, Rezvani A, Storb RF. Allogeneic hematopoietic cell transplantation: the state of the art. Expert Rev Hematol. 2010;3:285-99.
2. Appelbaum, FR. Hematopoietic-Cell Transplantation at 50. N Engl J Med. 2007;357:1472-5.
3. Zachary AA, Leffell, MS. Desensitization for solid organ and hematopoietic stem cell transplantation. Immunol Rev. 2014;258:183-207.
4. Abbas AK, Lichtman AH, Pillai S. Imunologia celular e molecular. 8th ed. Rio de Janeiro: Elsevier; 2015.
5. Brand A, Doxiadis IN, Roelen DL. On the role of HLA antibodies in hematopoietic stem cell transplantation. Tissue Antigens 2013; 81(1): 1–11.
6. Detrait M, Dubois V, Sohb M, Morisset D, Tedone N, Labussière H et al. Impact of anti-HLA antibodies on allogeneic hematopoietic stem cell transplantation outcomes after reduced-intensity conditioning regimens. Exp Hematol 2012: 40: 792–9.
7. Montgomery RA, Lonze BE, King KE, Kraus ES, Kucirka LM, Locke JE, et al. Desensitization in HLA-incompatible kidney recipients and survival. N Engl J Med. 2011;365:318-26.
8. Liwski R, Greenshields AL, Conrad DM, Murphey C, Bray RA, Neumann J, et al. Rapid optimized flow cytometric crossmatch (FCXM) assays: The Halifax and Halifaster protocols. Hum Immunol. 2018;79:28-38.
9. Gladstone DE, Bettinotti MP. HLA donor-specific antibodies in allogeneic hematopoietic stem cell transplantation: challenges and opportunities. Hematology Am Soc Hematol Educ Program. 2017;2017(1):645-650.
10. Ottinger HD, Rebmann V, Pfeiffer KA, Beelen DW, Kremens B, Runde V, et al. Positive serum crossmatch as predictor for graft failure in HLA-mismatched allogeneic blood stem cell transplantation. Transplantation 2002;73:1280-5.
11. Ansari M, Uppugunduri CR, Ferrari-Lacraz S, Bittencourt H, Gumy-Pause F, Chalandon Y, et al. The clinical relevance of pre-formed anti-HLA and anti-MICA antibodies after cord blood transplantation in children. PLoS One. 2013;8:e72141.
12. Ruggeri A, Rocha V, Masson E,Labopin M, Cunha R, Absi L, et al. Impact of donor-specific anti-HLA antibodies on graft failure and survival after reduced intensity conditioning-unrelated cord blood transplantation: a Eurocord, Société Franco-phone d'Histocompatibilité et d'Immunogénétique (SFHI) and Société Francaise de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) analysis. Haematologica 2013;98:1154-60.
13. Takanashi M, Atsuta Y, Fujiwara K, Kodo H, Kai S, Sato H, et al. The impact of anti-HLA antibodies on unrelated cord blood transplantations. Blood 2010;116:2839-46.
14. Kickler TS. The challenge of platelet alloimmunization: management and prevention. Transfus Med Rev. 1990; 4(4 Suppl 1):8-18.
15. van Marwijk Kooy M, van Prooijen HC, Moes M, Bosma-Stants I, Akkerman JW. Use of leukocyte-depleted platelet concentrates for the prevention of refractoriness and primary HLA alloimmunization: a prospective, randomized trial. Blood 1991; 77: 201–205.
16. Karpinski M, Pochinco D, Dembinski I, Laidlaw W, Zacharias J, Nickerson P. Leukocyte reduction of red blood cell transfusions does not decrease allosensitization rates in potential kidney transplant candidates. Journal of the American Society of Nephrology 2004; 15:818–824.
17. Ferreira AA, Zulli R, Soares S, de Castro V, Moraes-Souza H. Identification of platelet refractoriness in oncohematologic patients. Clinics 2011; 66: 35–40.
18. Kiefel V, König C, Kroll H, Santoso S. Platelet alloantibodies in transfused patients. Transfusion 2001; 41:766–770.
19. Sanz C, Freire C, Alcorta I, Ordinas A, Pereira A. Platelet-specific antibodies in HLA-immunized patients receiving chronic platelet support. Transfusion 2001; 41: 762–765.
20. Balduini C, Salvaneschi L, Klersy C, Noris P, Mazzucco M, Rizzuto F et al. Factors influencing post-transfusional platelet increment in pediatric patients given hematopoietic stem cell transplantation. Leukemia 2001; 15: 1885–1891.
21. Hatakeyama et al. Platelet transfusion refractoriness attributable to HLA antibodies produced by donor-derived cells after allogeneic bone marrow transplantation from one HLA-antigen-mismatched mother. Pediatric Transplantation 2011; 15:177–182.
22. Wang J, Xia W, Deng J, Xu X, Shao Y, Ding H et al. Analysis of platelet-reactive alloantibodies and evaluation of cross-match-compatible platelets for the management of patients with transfusion refractoriness. Transfus Med 2018; 28(1):40-46.
23. Yoshihara S, Maruya E, Taniguchi K, Kaida K, Kato R, Inoue T , et al. Risk and prevention of graft failure in patients with preexisting donor-specific HLA antibodies undergoing unmanipulated haploidentical SCT. Bone Marrow Transplant. 2012;47:508-15.
24. Ciurea SO, de Lima M, Cano P, Korbling M, Giralt S, Shpall EJ, et al. High risk for graft failure in patients with anti-HLA antibodies undergoing haploidentical stem-cell transplantation. Transplantation 2009;88:1019-24.
25. Gladstone DE, Zachary AA, Fuchs EJ, Luznik L, Kasamon YL, King KE, et al. Partially mismatched transplantation and human leukocyte antigen donor-specific antibodies. Biol Blood Marrow Transplant. 2013;19:647-52.
26. Costa LJ, Moussa O, Bray RA, Stuart RK. Overcoming HLA-DPB1 donor specific antibody- mediated hematopoietic graft failure. Br J Haematol. 2010;151:84-109.
27. Norlander A, Uhlin M, Ringden O, Kumlien G, Hausenberger D, Mattsson J. Immune modulation to prevent antibody-mediated rejection after allogeneic hematopoietic stem cell transplantation. Transplant Immunol. 2011;25:153-8.
28. Locke, JE, Zachary AA, Warren DS, et al. Proinflammatory events are associated with significant increases in breadth and strength of HLA-specific antibody. Am J Transplant. 2009;9:2136-9.
29. Leffell MS, Jones RJ, Gladstone DE. Donor HLA-specific Abs: to BMT or not to BMT? Bone Marrow Transplant. 2015;50:751-8.