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Donor Specific Antibodies in Hematopoietic Stem Cell Transplantation

Nahla A. M. Hamed*

Internal Medicine Department (Hematology Unit), Faculty of Medicine, Alexandria University, Egypt

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Corresponding author: Nahla A. M. Hamed, Internal Medicine Department (Hematology Unit), Faculty of Medicine, Alexandria University, Egypt

Abstract

Donor-specific anti-HLA antibodies (DSAs) represent a significant immunologic barrier in hematopoietic stem cell transplantation (HSCT). They are linked to primary graft failure, delayed engraftment, and poor survival. Patients with pre-existing DSAs had a markedly higher risk of graft rejection and non-relapsed mortality compared to DSA-negative recipients. The risk is particularly pronounced when DSAs are high-titer (mean fluorescence intensity >5,000) or complement-binding (C1q/C3d positive). Consensus recommendations of the American Society for Transplantation and Cellular Therapy (ASTCT) advocate for universal pre-transplant DSA testing, risk stratification based on antibody strength, and desensitization protocols (plasmapheresis, IVIG, rituximab, bortezomib, or daratumumab) to mitigate rejection risk.

Keywords: Donor-Specific Antibodies; Graft Failure; Mean Fluorescence Intensity; Desensitization; Matched Unrelated Donor

Abbreviations: DSAs: Donor-specific antibodies; HLA: human leukocyte antigen; GF: graft failure; MUD: matched unrelated donor; MMUD: mismatched unrelated donor transplantation; MFI: mean fluorescence intensity; AHCT: allogeneic hematopoietic cell transplantation; HHC: haploidentical hematopoietic cell transplantation

Introduction

Donor-specific antibodies (DSAs) are preformed recipient IgG allo-antibodies that are directed against human leukocyte antigen (HLA)- of the donor graft. They are targeting mismatched HLA antigens on the graft that are not shared with the donor and are resistant to the standard conditioning regimen [1]. DSAs are an important obstacle for transplantation in the HLA-mismatched setting, given the increased risk of primary graft failure (GF), delayed engraftment, and decreased survival [2]. A high incidence of GF is associated with the presence of DSAs in haplo-HSCT due to both higher grade of mismatch and the possibility of alloimmunization after pregnancies against offspring antigens in the case of female recipients, with prevalence between 10 and 20% that can reach more than 80% in female with multiple pregnancies [1]. There is also a relationship between anti-DPB1 DSAs and GF in matched unrelated donor (MUD) transplants and between DSAs and GF in both single and double cord blood transplants [1].

Risk factors for developing anti-HLA antibodies and DSA

The main causes of alloimmunization against HLA antigens are female sex, older age, prior receipt of cellular blood product transfusion, organ transplantation, and pregnancy [2]. The overall incidence of anti-HLA antibodies was greater among parous females than among males and nulliparous females. The prevalence of anti-HLA antibodies ranges from < 1% to 5% in healthy volunteers, 24.4% to 54.4% in pregnant women, and 23.2% to 32.8% in organ transplant candidates. A greater percentage of DSA-positive patients were diagnosed with acute myeloid leukemia (AML)/myelodysplastic syndromes (MDS) [3]. The incidences of anti-HLA antibodies are approximately 20–70% in haploidentical transplant modalities and 20–40% in unrelated donor or cord blood transplant settings [3].

Detection of DSAs

The screening for DSAs before MUD, mMUD, haplo and UCB transplant becomes mandatory [1]. For patients receiving unrelated donor trans-plantation, HLA-matching at least for HLA-A, -B, -C, and -DRB1 is preferred. However, recipients could potentially develop DSA against mismatches HLA-DQB1 and HLA-DPB1, which has been shown to significantly impact allograft outcome [4]. The gold standard for the detection of DSAs is solid-phase immunoassays (SPI) using the Luminex® platform [1]. Solid-phase immunoassays test antibodies in the recipient serum using purified HLA molecules, which conjugate to microtiter plates or to polystyrene beads.

After antibody-antigen complex formation, the solid plates or polystyrene beads are washed to remove unbound antibodies and conjugated secondary antibodies are added. The strength of HLA antibodies is reported as immunofluorescence intensity (MFI), that can be quantitatively analyzed using enzyme-linked immunosorbent assays or semi-quantitively by conventional flow cytometer or a fluoroanalyzer (LuminexTM) [4]. Moreover, the technique has also been modified to detect complement-fixing (C1q+ or C3d) antibodies [1]. This method is semi-quantitative (via antibody titers), convenient, and has higher sensitivity and specificity compared to cell-based assays [4].

Limitations of this Method Include

The detection of bead-bound non-HLA antibodies, false positives resulting from manufacture-related conformational changes in HLA molecules ("cryptic epitopes"), and false negative results or falsely low antibody levels due to the "inhibition effect" (sometimes inaccurately referred to as "prozone effect"), a phenomenon that involves interferences with binding of fluorescent-dye-conjugated secondary antibodies due to high levels of HLA antibodies [4].

Treatment of Patients with DSA before Transplant

Transplantation using hematopoietic stem cells from a donor without corresponding HLA antigens is an ideal option. However, this might not always be possible due to the limitation in donor availability and an urgent need to proceed to transplant [5]. If no alternative donor source is available, the best option is desensitization of the recipient to decrease total antibody load to levels that would permit successful donor stem cell engraftment. Existing literature on HLA desensitization has primarily focused on haploidentical transplant, and there is a lack of experience regarding the optimal strategy in UCB transplantation [2].

Several desensitization methods have been used. These strategies are classified into the following 4 strategies:

i. antibody removal by using plasmapheresis or immunoabsorption;

ii. inhibition of antibody production by using monoclonal antibodies to CD20+ B lymphocytes (rituximab), and proteasome inhibitor against alloantibody producing plasma cells (bortezomib);

iii. 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

iv. inhibition of complement cascade.

Plasmapheresis is the most common method of desensitization used in AHCT patients. More recent protocols use combination of plasmapheresis and other methods, which aim to inhibit antibody production and antibody neutralization such as IVIg and rituximab. Other regimen was a combination of plasmapheresis, rituximab, antibody adsorption with platelets and administration of the proteasome inhibitor, bortezomib. Even though this protocol could reduce the risk of GF, additional immunologic suppression after stem cell infusion could increase the risk of disease relapses since the treatment could potentially affect T cells in the infused stem cell product [4].

- For DSA >20,000 MFI, patients may require antibody titration (due to bead saturation). An alternative donor without corresponding HLA should be selected or should be treated using an investigational approach [4].

- For DSA up to 20,000 MFI, plasmapheresis, rituximab, IVIG and infusion of donor-derived HLA antigen (either irradiated buffy coat for the corresponding HLA class I and II or platelet transfusions for corresponding HLA class I only) are recommended [4].

- For DSA 2,000-10,000 MFI in haploidentical HSCT or 1,000- 10,000 MFI in CBT, patients can be treated with a lower intensity desensitization protocol, such as rituximab with IVIG.

Post-desensitization DSA levels should be measured to monitor clearance; additional intervention may be needed if elevated levels persist before neutrophil recovery [4].

Some of these interventions have been used in HHCT and mismatched donor hematopoietic stem cell transplantation. However, most published data regarding transplant outcomes in AHCT patients receiving these desensitization methods are case reports or small studies with limited number of patients and variety of graft outcomes [5]. Daratumumab is a fully human IgG1-kappa, CD38 antibody. The ability of daratumumab to induce depletion of plasma cells and immune regulation permitted it to be a new agent in therapeutic armamentarium for DSA desensitization. It has already been utilized in solid organ transplantation recipients with anti HLA and DSA. Reports on the use of this agent in mismatched allo-SCT are limited. The use of daratumumab for DSA was found to be a safe and effective desensitization regimen in positive HLA mismatched patient in one study [6].

How to monitor treatment and DSA levels after desensitization and transplant?

It is recommended that:

- Anti-HLA antibodies testing should be part of the pre-HSCT work up [4].

- DSA should be monitored before and after completing desensitization, as well as within 1 month before starting conditioning regimen and one day before stem cell infusion (day-1) [4] in all candidates of HSCT (related, unrelated or cord blood grafts) with mismatched HLA antigens or alleles [4] to determine

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clearance of antibodies [5].

- C1q testing is recommended before and after desensitization for patients with DSA>2,000 MFI in haploidentical HSCT (or >1,000 MFI in single CBT) [4].
- If DSA >1,000 MFI in the absence of an alternative suitable donor, it is recommended that patients undergo desensitization therapy, especially with high DSA levels (>5,000 MFI) and/or C1q positive, which pose a very high risk to the allograft [5]. Additional desensitization may be needed in patients with persistently high DSA or those experiencing increasing DSA levels after stem cell infusion [4].
- The choice of desensitization protocol may be based on prior local experience [5].
- Monitoring of DSA levels is recommended weekly thereafter until clearance, as DSA levels will not clear immediately after treatment and/or stem cell infusion. Patients with C1q+ should continue to have C1q testing with repeat DSA serum samples until negative [5].
- DSA monitoring after stem cell infusion is recommended at least weekly until engraftment and/or DSA<2,000MFIs. Additional testing may be needed in patients with DSA with poor graft function or secondary graft failure [4].
- Enough evidence has been generated for uniform testing and treatment for patients with DSA prior to haploidentical stem cell transplantation [5].

Conclusion

DSAs are a leading cause of graft failure in HSCT. Universal pre-transplant screening is now standard of care. High-titer or complement-binding DSAs require aggressive desensitization before proceeding with transplant.

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