Annals of Stem Cell Research & Therapy

Review Article
Published: 26 Nov, 2018

A Review of Isoagglutinin Change Kinetics in ABO Incompatible Hematopoietic Stem Cell Transplantation

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Abstract

Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) is a treatment modality for high-risk hematological malignancies that has considerably evolved over time. ABO incompatibility (major, minor or both) has never been considered as a contraindication for HSCT, since ABO antigens are not expressed in the hematopoietic stem cells. In fact, near 40% to 50 % of all HSCT has some degree of ABO incompatibility and ABO mismatch does not have relevant impact on transplantation outcome. Some known immuno hematologic complications arising after transplantation are related to hematic and seric ABO group changes in ABO incompatible HSCT. Pure Red Blood Cell Aplasia (PRCA) occurs in major incompatibility and is due to unexpected persistence of recipient isoagglutinins directed against donor Red Blood Cell (RBC) antigen long time after HSCT. Passenger lymphocyte syndrome occurs in minor incompatibility and is explained by an immune but transient response by the donor lymphocytes producing isoagglutinins against recipient RBCs. On the contrary, if isoagglutinins are directed to ABO antigens absent in donor and recipient RBCs, hemolytic complications do not occur. Little information is available about the isoagglutinin evolution after different HSCT modalities and in some cases contradictory results are reported. The objective of this article is to update the knowledge regarding the donor and recipient isoagglutinin titers kinetics after ABO incompatible HSCT and review the clinical conditions that can be associated.

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Received Date: *20 Oct 2018*
Accepted Date: *23 Nov 2018*
Published Date: *26 Nov 2018*

Citation:
Alcaina PS. A Review of Isoagglutinin Change Kinetics in ABO Incompatible Hematopoietic Stem Cell Transplantation. Ann Stem Cell Res Ther. 2018; 2(4): 1025.

Introduction

Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) is a treatment modality for high-risk hematological malignancies that has considerably evolved over time. Since first experiences using bone marrow, new stem cell sources as peripheral blood and cord blood were subsequently introduced [1-5]. Human Leukocyte Antigens (HLA) matching plays a critical role in the transplantation outcome and is used as the main criteria for donor selection. Strict assessment of HLA match status of family members or voluntary donors is mandatory in order to identify a suitable related or unrelated donor [6]. Haploidentical HSCT is a raising strategy to circumvent the lack of related HLA identical donors [7,8]. ABO incompatibility has never been considered as a contraindication for HSCT, since ABO antigens are not expressed in the hematopoietic stem cells [9]. In fact, near 40% to 50 % of all HSCT has some degree of ABO incompatibility and ABO mismatch does not have relevant impact on transplantation outcome [10-13]. Major ABO incompatibility occur when the recipient has anti-A or anti-B natural antibodies against A or B antigens expressed on donor Red Blood Cells (RBCs). In the case of ABO minor incompatibility, the anti-A or anti-B antibodies are present in the donor plasma and directed against recipient ABO RBC antigens. Bidirectional incompatibility shares major and minor ABO incompatibility features [11]. Theoretically, after the transplantation, the recipient-derived antibodies disappear due to the effect of conditioning chemotherapy and are progressively replaced by antibodies produced by engrafted donor B cells. Then, isoagglutinin titers probably reflect immuno hematological reconstitution after HSCT. As the engraftment occurs, the appearance of donor red blood cells is detected. However, the recipient isoagglutinin disappearance kinetics does not occur in the same manner and could be influenced by conditioning chemotherapy (myeloablative versus reduced intensity), stem cell source (bone marrow, peripheral blood, umbilical cord blood) and HLA matching degree (matched, mismatched). When there is a coincidence of anti-A/B isoagglutinins (in donor or recipient) and RBCs expressing the specific ABO antigen against which the isoagglutinins are directed (in donor or recipient), hemolysis can occur. Some known immuno hematologic complications arising after transplantation are related to hematic and seric ABO group changes in ABO incompatible HSCT. Pure Red Blood Cell Aplasia (PRCA) is a complication of ABO major incompatibility and is due

to unexpected persistence of recipient isoagglutinins directed against donor RBC antigen long time after HSCT. Passenger lymphocyte syndrome occurs in ABO minor incompatibility and is explained by an immune but transient response by the donor lymphocytes producing isoagglutinins against recipient RBCs [14-16]. On the contrary, if isoagglutinins are directed to ABO antigens absent in donor and recipient RBCs, hemolytic complications do not occur. Little information is available about the isoagglutinin evolution after different HSCT modalities and in some cases contradictory results are reported. The objective of this article is to update the knowledge regarding the donor and recipient isoagglutinin titers kinetics after ABO incompatible HSCT and review the clinical conditions that can be associated. Following the classification of isoagglutinins established by Lee et al., [17], we have reviewed in first place recipient derived isoagglutinins produced against donor RBC antigens, in second place the isoagglutinins that are produced by donor B cells against recipient RBC antigens, and in last place isoagglutinins produced by donor or recipient but directed against ABO antigens absent both in donor and recipient.

Recipient Derived Isoagglutinins against Donor Red Blood Cell Antigens (RDIS) in ABO Major Incompatibility

There is only one study that analyzed the isoagglutinin titers in a sequential manner in ABO incompatible HSCT [17]. In this report authors reviewed 62 HSCT, 51 from bone marrow and 11 from peripheral blood, 40 of them with major ABO mismatch. RDIs disappeared by 89 days after transplantation as median. The probability of RDIs disappearance by 1 year was 97.3%. Unrelated donor transplantation and Acute Graft Versus Host Disease (aGVHD) were factors significantly associated to a more rapidly disappearance of isoagglutinins. The genetic disparity between the donor and recipient could accelerate clearance of RDIs, as suggested by the authors. Ten patients who developed PRCA had a median time to isoagglutinin disappearance of 209 days, as compared to 60 days in patients who did not developed PRCA [17]. Other reports showed that RDIs titers decline more slowly after reduced-intensity conditioning peripheral blood HSCT as compared to myeloablative chemotherapy peripheral blood HSCT [18,19]. Four cases of PRCA were detected among the 14 major ABO incompatible HSCT with low intensity conditioning regimen while there were no cases of PRCA among 12 patients who received a myeloablative HSCT. These authors observed that RDIs and plasma cells persist after T, B and myeloid cells have disappeared, concluding that host plasma cells are the primary source of isoagglutinins production causing PRCA after major ABO incompatible HSCT with reduced intensity conditioning chemotherapy [19]. Other authors have also confirmed a delay disappearance of RDIs in patients who received a reduced intensity myeloablative HSCT. The chemotherapy conditioning regimen administered before HSCT usually eliminates the recipient B lymphocytes [20]. However, in some cases the conditioning regimen is less intensive and does not completely eliminate the hematopoietic system of recipient [21]. Persisting B lymphocytes and plasma cells can continue to secrete anti A/B for up a year, producing post transplant PRCA [18]. The prolonged persistence of RDIs was also associated to a more RBC transfusion requirements [20]. The resolution of PRCA occurred after reinforcement of graft versus host effect by reducing immunosupression or donor leukocyte infusion, supporting a graft versus plasma cell effect [20]. Stussi et al., [22] analyzed isoagglutinin titers in 32 patients undergoing allogeneic HSCT, 18 of them with major ABO incompatibility. They found the disappearance of RDIs within weeks after major ABO incompatibility and did not reappear in the further post-transplant course. Mielcarek et al., [23] reported the median time after bone marrow HSCT needed to undetection of IgG/IgM isoagglutinins was shorter for HLA matched unrelated donor HSCT (median 46 days) than for HLA-matched related donor HSCT (median 61 days). Patients who developed aGVHD also had a quicker isoagglutinin disappearance. This fact is interpreted by authors as the host-directed donor T cells in unrelated donors lead to more rapid elimination of residual antibody producing host cells and plasma cells as compared to related HSCT donors. Then there is again evidence for a graft versus plasma cell effect. Removal of persisting isoagglutinin by plasmapheresis or immunoadsorption has been tried with success as treatment for PRCA [24,25]. Our group retrospectively reviewed 36 patients who had undergone a major ABO incompatible HSCT at our Institution (La Fe University Hospital, Valencia) and determined their hematic and seric ABO group and isoagglutinin titres. The source of the progenitors was Umbilical Cord (UCB) in 11 patients and peripheral blood (PBSCT) in 25 [26]. Two patients who received a myeloablative peripheral blood HSCT developed a PRCA related to the persistence of RDIs. The first patient´s original blood group was B+ and the donor´s blood group was AB+. The second patient´s original blood group was O+ and the donor´s blood group was A+. In both cases, anti-A was involved and donor chimerism in T-cell fraction was always 100%. Patients presented a PRCA from the immediate post-transplant period until 386 and 230 days after transplantation, respectively, with blood transfusion dependence. The anti-A isoagglutinin titer was 2 in the first case and 4 in the second. Recovery of PRCA was associated to RDIs disappearance.

Donor Derived Isoagglutinins against Recipient Red Blood Cell Antigens (DDIS) in ABO Minor Incompatibility

In 1977, How et al., [27] reported six cases of hemolytic anemia attributed to DDIs after allogeneic Bone Marrow Transplantation (BMT). These authors detected DDIs in 15 of 18 patients who underwent BMT, although only 3 of 21 developed clinically significant hemolysis. DDIs (anti-A in four cases, anti-B in 1 case) were developed one to three weeks after BMT. The study by Lee et al., [17] detected DDIs in five of 36 (13.8%) patients who received a minor ABO incompatible HSCT. Only in one patient the DDIs were detected before disappearance of recipient RBCs without hemolysis. It has to be highlighted that most patients in this study received bone marrow grafts. Snell et al., [28] detected DDIs against recipient RBC in 15 of 24 (62.5%) patients who received peripheral blood HSCT. Of these patients, 7 developed severe but self-limited hemolysis requiring RBC transfusions. The detection of DDIs ranged from 6 to 88 days after HSCT. Contrarily, these authors failed to detect DDIs in 14 patients who underwent a umbilical cord blood HSCT, concluding that differences in the maturational state of the B lymphocytes in the UCB and peripheral blood grafts could explain these differences [28]. Greater number of B lymphocytes is present in peripheral blood grafts than in bone marrow and umbilical cord blood grafts [29]. These authors question if B cells from umbilical cord blood grafts ever make any isoagglutinin. Our Group has showed long term production of IH against recipient red blood cell antigens can occur after UCBT [30]. One A positive patient who had received an O positive UCBT more than 10 years ago, was erroneously transfused with recipient ABO group (A positive), without any adverse effect. However, after transfusion we detected anti-B and anti-A titer of

256 and 2024 respectively. This is the only case in which IH against recipient RBC was detected. Then, the B cells from the umbilical cord blood graft are capable of producing anti host isoagglutinins when they receive antigenic stimuli. Of 189 patients most of them transplanted with a bone marrow stem cell graft, Igarashi et al., [30] showed production of DDIs in 36 (19%) at a median of 13 days after HSCT. A Strong correlation between DDIs production and aGVHD development was found, suggesting that DDIs production could be useful as predictor of subsequent aGVHD after ABO incompatible HSCT. All patients who developed grade IV aGVHD showed a DDIs titer 4. In this study none of the patients who received UCBT showed any isoagglutinin production [31]. It has been shown that B cells has a defect in the developmental and functional recovery after UCBT due to a high proportion of immature transitional B cells with insufficient CD40 mediated signals [32]. Chung et al., [33] found a significant correlation between DDIs and aGVHD. The patients, who had aGVHD and DDIs, developed the DDIs before day 60 post transplantation more frequently and the period of elevation was shorter than patients who did not develop aGVHD. Zaimoku et al., [34] monitored IgM and IgG anti-recipient ABO antigens in 18 consecutive patients with hematological malignancies undergoing HSCT. Five of them (28%) developed a transient immune hemolysis associated with the detection of IgM and IgG anti recipient ABO antibodies after a median of 16 and 22 days after HSCT respectively. All five patients developed aGVHD grade II-IV. Authors suggest that IgM anti recipient ABO antibody may be an early predictor of aGVHD and poor survival.

Recipient or Donor Derived Isoagglutinins against ABO Red Blood Cells absent Both in Donor and Recipient in ABO Minor or Major ABO Incompatibility

Lee et al., [17] have shown that titers of isoagglutinins against ABO antigens absent in both donor and recipient red blood cells decreased post transplant, and then rose again by day 59. This fact suggests that there is a transition from isoagglutinin production by recipient B cells to production by maturing donor B cells. After HSCT, most patients develop long term donor derived isoagglutinin against red blood cell antigens that are not present in recipient. Our group reported the long term presence of donor derived isoagglutinins in patients undergoing minor ABO incompatible cord blood and peripheral blood HSCT [30]. Sixteen patients who received an UCBT developed donor derived isoagglutinins in different titers ranging 4 to 512, the anti-A/B antibodies were detected from 132 to 5067 days after HSCT, and none of patients except one produced isoagglutinins against recipient red blood cells (RBC). Therefore, donor isoagglutinins against recipient RBC are not routinely produced in minor incompatible HSCT, probably due to the development of tolerance of B cells or immunosuppressive treatment. In experiences with mice, Tomita et al., [35] based on experiences in mice suggest that after receiving minor ABO incompatible bone marrow transplantation, B cells derived from engrafted donor precursor cells were induced tolerance to recipient specific antigens.

Conclusion

Isoagglutinin changes after ABO incompatible HSCT are directly related to immuno hematologic complications that may worsen the transplantation outcome, as passenger lymphocyte syndrome and pure red cell aplasia. Isoagglutinin kinetics is often unpredictable but provides valuable information about the course of transplantation and alert about the complications that can arise as aGVHD and hemolysis. Therefore, transfusion services should monitor isoagglutinins in a sequential manner after ABO incompatible HSCT and clinicians should be take into account this data in order to make accurate assessment of immuno hematological complications.

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