# AB0-incompatible allogeneic hematopoietic stem cell transplantation

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## Introduction

Due to the fact that the human leukocyte antigen (HLA) system is inherited independently of the blood group system, approximately 40-50% of all hematopoietic stem cell transplants (HSCT) are performed across the AB0-blood group barrier.[1,2] Three groups of AB0 incompatibility do exist: minor incompatibility (in 20-25% of transplants) is characterized by the ability of donor B lymphocytes to produce anti-recipient isoagglutinins (e.g. group O donor to a group A recipient). In contrast, major incompatibility (in 20-25% of transplants) is characterized by the presence of anti-donor isoagglutinins (e.g. group A donor to a group O recipient). Bidirectional AB0-incompatibility (up to 5% of transplants) occurs when both donor and recipient produce isoagglutinins against each other (e.g. group A donor to a group B recipient).

## Hemolysis

Due to the immunological incompatibility between donor and recipient hemolytic transfusion reactions can appear. According to the time of occurrence a distinction can be made between immediate (during graft infusion) and delayed (during engraftment) immune hemolysis. In AB0-incompatible bone marrow transplant (BMT), it is clinical routine either to remove isoagglutinins (minor incompatibility) or incompatible red blood cells (RBCs) from the graft (major incompatibility) or to reduce anti-donor isoagglutinins in the recipient to avoid immediate hemolysis by various techniques (Table 1).[3,4]

Due to a lesser content of RBCs and plasma in peripheral blood progenitor cell (PBPC) concentrates it is not usually necessary to perform a manipulation of these grafts.

With the introduction of reduced intensity conditioning (RIC) regimens and the associated graft-versus-host disease (GvHD) prophylaxis an increased incidence of severe delayed immune hemolysis in minor AB0-incompatible HSCT has been observed.[5-7] The reasons for this complication are thought to be a higher amount of remaining recipient RBCs due to the reduced dose of conditioning, enhanced isoagglutinin production by donor B-lymphocytes and GvHD prophylaxis regimens without methotrexate (MTX). The incidence of delayed hemolysis after RIC in the literature varies between 5 and 30% and can be attributed to differences in post-grafting immunosuppression.[5-7] After transplantation of PBPCs into an AB0-mismatch host, isoagglutinin-producing B cells might escape T-cell control when T-cell activation is blocked exclusively by CsA. Immunosuppressive agents such as the antimetabolites methotrexate or mycophenolate mofetil (MMF) inhibit proliferation of T and B lymphocytes and antibody production. The circulating $t_{1/2}$ of MMF is only 3.6 hours, and the bond to inosine monophosphate dehydrogenase is rapidly reversible. This may permit antigen-primed B cells to escape T-cell control.[8]

## Engraftment

Another immunological based phenomenon is the occurrence of pure red cell aplasia (PRCA) with an incidence of 15-20% after major AB0-incompatible transplantation. Isoagglutinin producing plasma cells are terminally differentiated and therefore relatively resistant to chemo- and radiotherapy. Plasma cells surviving the conditioning regimen are responsible for the inhibition of the growth of RBC precursors in the bone marrow.[9-11]

In terms of neutrophil and platelet engraftment the vast majority of studies found no significant difference between AB0-identical and AB0-mismatched transplant recipients.[10-12] A report by Kimura *et al.* for the

**Table 1. Standard procedures for AB0-incompatible transplants and transfusion policy.**

| *AB0-mismatch* | *BM graft manipulation* | *Therapeutic apheresis* | *Transfusion policy* |
|---|---|---|---|
| Major | RBC-depletion | Plasma-exchange with AB plasma or albumin/sodium when anti-donor hemagglutinins are > 1:16 | Group 0 RBC until anti-donor hemagglutinins are undetectable, then switch to donor blood group |
| Minor | Plasma-depletion when anti-recipient hemagglutinins are > 1:128 | Experimental: RBC exchange with group 0 RBC | RBCs of donor blood group |
| bidirectional | RBC-depletion and plasma-depletion (when anti-recipient hemagglutinins are > 1:128) | | Group 0 RBC until anti-donor hemagglutinins are undetectable, then switch to donor blood group |

*BM = bone marrow, RBC = red blood cells.*

Japan Marrow Donor Program, published elsewhere in this journal, documented not only a delayed recovery of RBCs but also of neutrophils and platelets in 1,384 patients receiving a major AB0-incompatible unrelated bone marrow graft.[13] This phenomenon has also been previously reported by other authors to be limited to major AB0-incompatible transplantation, speculating that anti-donor isoagglutinins bind to A or B antigens absorbed on the surface of neutrophils or their precursors.[14-16] Remberger *et al.* observed an increased risk of graft failure after major AB0-incompatible transplantation (7.5% *vs*. 0.6%) in an analysis of 224 patients.[15] However, in their analysis, HLA-A, -B, -DR allele level mismatch was also a factor significantly associated with graft failure. Five of their 6 patients with graft failure had at least one HLA allele mismatched graft making it difficult to precisely ascribe the definitive role of AB0-incompatibility in this setting.

### Graft-versus-host disease

Most publications show no influence of AB0-mismatch on the incidence of clinically significant acute GvHD.[6,11,14]

The Seattle group found no influence of AB0-mismatch on the incidence of GvHD in matched related (MRD) and unrelated transplants (MUD): the overall incidence of acute GvHD II-IV was 47% in MRD (n=918) and 83% in MUD (n=748).[11] Within the group of MRD transplants, the incidence of acute GvHD in recipients of AB0 matched, major, minor, and bidirectional mismatched marrow was 47%, 45%, 43%, and 60% $p$=0.22 for AB0-matched *vs.* mismatched respectively. Among MUD allografts, the corresponding incidence was 83%, 83%, 85%, and 82% ($p$=0.81), respectively. However, some authors raise the question whether AB0 antigens and isoagglutinins are also involved in the pathogenesis of GvHD. AB0 antigens show a broad distribution, and are also expressed on endothelial cells and von Willebrand factor. They suggest that isoagglutinins can bind to host endothelial cells and potentially trigger GvHD.[12] Kimura *et al.* report a higher incidence of acute GvHD III-IV in both the major and minor AB0-mismatch group. Interestingly, the incidence of liver GvHD was higher in minor AB0-incompatible transplantation. Their hypothesis is that epithelial cells of large bile tract expressing AB0 antigens may be injured by donor derived isohemagglutinins, thereby possibly increasing the incidence and severity of liver GvHD.[13]

### Transplant-Related Mortality (TRM)

As regards TRMs published results are controversial. Whereas in large series no significant difference in terms of TRM between AB0-matched and AB0-mismatched recipients was reported,[11,14,15] other investigators did find such differences: in a large series of 5,549 unrelated BM transplant recipients of the Japan Marrow Donor Program published elsewhere in this journal, minor and major AB0 incompatibility significantly increase the risk of TRM.[13] Bolan *et al.*, in a smaller series, report massive immune hemolysis as potentially life threatening after minor AB0-incompatible HSCT.[5] In addition, we in our series also found severe immune hemolysis in the AB0-minor mismatch setting to be an important trigger of TRM.[6]

Taken together, the importance of AB0-incompatibility for the overall clinical outcome following allogeneic HSCT is still unclear. However, various investigators have found an influence of AB0-incompatibility on transplant-related morbidity. This leads to the question whether preventive strategies to avoid this complication should be taken.

If possible, an AB0-identical donor should be chosen. Several standard procedures for AB0-incompatible transplants are already being used (Table 1). Furthermore, in the minor AB0-incompatible setting, a partial red blood cell exchange before transplantation can lead to an amelioration of symptoms making it an attractive tool especially after reduced intensity conditioning.[8]

Several questions in this setting still remain unanswered, e.g. the outcome of patients after bidirectional AB0-incompatible transplantation where data are very sparse. Whether recently developed conditioning and GvHD prophylaxis regimes will affect the clinical outcome of AB0-incompatible transplanted patients remains to be seen.

AB0-incompatibility in allogeneic stem cell transplantation will remain a challenge both for the transplant physician and the specialist for transfusion medicine; elaboration of standards for transfusion policy in this setting seems mandatory.

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## Hematopoietic stem cell transplantation: 40 years of continuous progress and evolution

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The importance of an innovative medical event can be measured by the insights and the clinical consequences that the event itself produces for the benefit of human beings. In this regard, there is no doubt that hematopoietic stem cell transplantation (HSCT) has represented one of the most innovative treatments of the last decades, as well as one of the most significant medical feats of human bio-solidarity. This year is the right time to celebrate a significant anniversary of HSCT, as the first two successful transplants were performed just 40 years ago, in 1968.[1,2] The first patient had a form of sex-linked lymphopenic immunological deficiency, and, at five months of age, was transplanted with bone marrow (BM) cells of his sister, aged eight years.[1] The second was a child with Wiskott-Aldrich syndrome, who, at the age of two years, received the allograft from a sister, herself an X-trisomic (47, XXX) child.[2] The demonstration of histocompatibility between donor and recipient was obtained through the tests of mixed lymphocyte culture, and of lymphocytotoxic assay in the first case,[1] while in the second pair, the reciprocal non-stimulation between the patient's lymphocytes and those of his sister was verified repeatedly, also with extensive controls.[2]

Behind this accurate attention paid to histocompatibility between donor and recipient, which was emphasized in both scientific reports, we find the following observation of Bach and colleagues:[2]

"*In all reported cases of bone-marrow transplantation in man, the histocompatibility relationship between donor and recipient has not been well defined. Proven chimerism following bone-marrow transplantation in man has been rare.*"

The following remark of Gatti and colleagues about a lack of histocompatibility, in the case of previous transplants performed on patients with lymphopenic immunological deficiency, provides a rather similar concept:

"*Unfortunately, the introduction of allogeneic immunologically competent cells has consistently produced fatal graft-versus-host reactions because patients with this disease, being unable to reject the grafted immunologically competent cells, cannot prevent an immunological assault by the donor lymphocytes on the host's cells and tissues*".[1]

If, certainly, HLA identity in the donor/recipient pair was deemed an essential condition, which could not be eluded before a transplant could be programmed, there was another prerequisite to be satisfied for an allograft to be successful, namely the need to administer to the transplanted subject, despite the demonstrated HLA identity with the donor, an immune suppressive drug able to prevent the attack of donor immune cells on recipient tissues, what is widely known as graft-versus-host disease (GvHD) prophylaxis. This prophylaxis of HSCT-related immune complications, together with careful monitoring of the clinical signs heralding GvHD, in turn permitting a prompt start of an immune suppressive treatment whenever needed, was immediately recognized as a key element for successfully transplanting humans.[1]

Today, after 40 years of unceasing progress, full HLA identity between donor and recipient remains mandatory in cases of unmanipulated BM or peripheral blood stem cell (PBSC) transplantation, but we have also learned how to cross the HLA barrier, through the use of megadoses of $CD34^+$ cells, coupled with profound T-cell depletion of the graft,[3] or through the use of unrelated donor cord blood transplantation (CBT).[4] This year is, by the way, also the twentieth anniversary of CBT, which was first successfully performed by Eliane Gluckman and colleagues in Paris on an American child with Fanconi anemia, using the cryopreserved cells of