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REVIEW ARTICLE

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ABO-incompatible organ and bone marrow transplantation: current status

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Abstract Despite the presence of preformed antibodies against AB oligosaccharide epitopes on the donor vascular endothelium, approximately one-third of ABO-incompatible organ allografts are not rejected by a humoral mechanism. With the growing immune-manipulation of the recipient, survival rates can be raised considerably, although they remain significantly inferior to those of ABO-compatible transplantation. Data from the Collaborative Transplant Study indicate a 1-year graft survival rate of approximately 50–60% following cadaveric ABO-incompatible kidney, liver or heart transplantation, compared with 70–80% for an ABO-compatible organ. The results for infants and young children, however, are very much better than those of adults, particularly for liver and heart transplantations, and the data suggest that B-cell tolerance can develop in the infant age group. We here review clinical and experimental experience with ABO-incompatible organ and bone marrow allotransplantation and address the mechanisms by which organs or cells survive in the presence of natural anti-carbohydrate antibodies.

Keywords ABO-incompatibility · Accommodation · B-cell tolerance · Bone marrow allotransplantation · Organ allotransplantation · Tolerance

Introduction

ABO blood group-incompatible (i.e., major-mismatched, e.g., A to O) organ and bone marrow (BM) transplantation (Tx) can be successfully performed in the clinical setting. Approximately one-third of ABO-incompatible organ allografts are not rejected by an antibody (Ab)-mediated mechanism and survive as long as ABO-compatible (i.e., identical, e.g., A to A, or minor-mismatched, e.g., O to A) grafts, even when no specific therapy is administered. In the majority of patients undergoing ABO-incompatible alloTx, however, a preparative regimen that includes depletion of anti-AB Abs from the host and/or intensive immunosuppressive therapy is required to prevent humoral rejection. Despite this therapy, Ab-mediated rejection still occurs in some cases, leading to loss of the graft. In the remainder, long-term acceptance of the graft is observed. In some cases, production of Abs directed against antigens on the graft vascular endothelium is subsequently suppressed, which suggests that B-cell tolerance had been induced. In others, Ab levels return to baseline or even supra-normal levels and yet the graft is unaffected. Graft survival in the presence of specific Ab directed against antigen determinants on the graft vascular endothelium, in the presence of normal levels of complement, is known as 'accommodation'.

ABO blood group system

ABO antigens are oligosaccharide structures that are present on the surface of red blood cells (RBCs), the

vascular endothelium, and on certain other kinds of tissue in the human body [1]. Expression has been reported to be variable in different tissue types; for example, the heart is estimated to express fewer ABO antigens than some other kinds of tissue [1]. Individuals with blood group A can be grouped into such with high-density (A1) or low-density (A2) expression of the antigen, which is due to differences in the glycosyltransferase, the enzyme that adds the sugar residue to the H epitope. Between 8% and 25% of people with blood group A are of type A2 [2]. Because of the difference in antigen expression, most anti-A isohemagglutinins bind strongly to the A1 antigen, but not to A2. Therefore, Tx of an A2-incompatible organ is less likely to be associated with Ab-mediated rejection, and is frequently followed by long-term graft survival.

Preformed natural Abs (isohemagglutinins) against AB antigens are present at birth as IgG as a result of diaplacentaric transport of maternal Abs, but not as a result of self-production. Maternal Abs disappear from the neonate after 2 weeks, but at approximately 8–12 weeks the newborn infant starts producing IgM and IgG of its own [3]. Adult levels are reached by the age of 5–10 years [4]. Although the stimulus for the production of Ab to A and/or B determinants remains uncertain, one commonly held hypothesis is that it is a response to the presence of A and/or B saccharides on bacteria or other microorganisms that colonize the infant gastrointestinal tract [4, 5, 6].

In addition to the ABO blood groups, several other blood group antigens have been demonstrated on blood cells and/or various tissue types. Few reports on their relevance to Tx exist, but their influence on allograft survival is clearly minimal [7]. A relationship between secretor status and allograft survival has been discussed, but definite conclusions are lacking [8, 9].

Organ transplantation across the ABO barrier

Approximately one-third of organ transplantations performed across the ABO barrier (i.e., ABO-incompatible) undergo no form of Ab-mediated rejection and experience no greater incidence of acute cellular rejection than ABO-compatible grafts [10]. The reasons remain uncertain, but may be related to factors such as the extent of antigen expression on the graft and/or the titer of Ab in the patient. ABO-compatible, but mismatched grafts, e.g., O to A, are associated with outcomes equivalent to those of ABO-matched transplants. In the remainder of ABO-incompatible transplants, humoral rejection is frequent, especially within the first 30 days [11]. It may progress rapidly and is sometimes resistant to treatment. However, a direct correlation between Ab titers and humoral rejection, although strongly suggested, remains inconclusive [11, 12]. Data from the Collaborative Transplant Study (CTS; kindly provided by Dr Gerhard Opelz in 2001) indicate a 1-year graft survival rate of approximately 50–60% following cadaveric ABO-mismatched kidney, liver or heart Tx (often in the presence of intensified immunosuppressive therapy), compared with 70–80% for an ABO-matched organ.

Kidney

An ABO-incompatible kidney Tx was first reported by Hume, Murray and Starzl, and their respective colleagues in 1955, 1960, and 1964, respectively [13, 14, 15]. Although long-term survival of the grafts was observed in some initial cases, overall experience indicated that hyperacute rejection could occur. Nevertheless, due to the limited availability of organs, a significant number of ABO-incompatible kidney transplantations have been performed, especially in the field of living-related Tx [16, 17, 18, 19, 20, 21, 22]. CTS data indicate for cadaveric ABO-incompatible grafts a 1-year survival rate of 64%, compared with 83% for ABO-compatible grafts. In this review, attention will be directed to the larger series, with emphasis on the more recent reports.

Antibody-mediated rejection of ABO-incompatible renal allografts can arbitrarily be divided into two subtypes—hyperacute (occurring within 24 h) and acute humoral rejection (generally occurring within 30 days) [11]. In hyperacute rejection, either no urine is produced or there is a dramatic reduction within hours. This is usually associated with reductions in the platelet count, Abs, and complement (C3, C4) values. Humoral rejection is marked by a progressive development of venous congestion and arterial and glomerular thrombosis, associated with interstitial edema and hemorrhage.

A1-incompatible kidney transplantation

The relationship between graft survival and anti-AB Ab levels remains somewhat controversial. In early reports, the disappearance of Abs after Tx was attributed to adsorption on to the graft, since, in some cases, Abs reappeared after graftectomy [23, 24, 25]. The concept of depleting anti-AB Abs was probably first introduced by Slapak et al. in 1981 [26] when a patient was treated with plasmapheresis for rejection. Subsequently, the same group reported on pre-Tx immuno-adsorption and plasmapheresis for ABO-incompatible Tx [27], followed by a high survival rate of 87%. By the late 1980s, ABO-incompatibility was considered to be a barrier to alloTx, and it was believed that only appropriate pretreatment of the patients by Ab elimination and splenectomy could lead to long-term success [12]. Patients who maintained low Ab titers post-Tx were reported to have better outcomes than those with high titers [12, 22, 24, 28, 29,

30]. In the majority of the reports, pre-Tx removal of Abs (to 1:2–1:8) as well as maintenance of low post-Tx titers (1:4–1:16) is preferred [31].

Alexandre et al. reported their pioneering experience in 37 patients in 1987 [12] with focus on allograft survival and its relationship to preformed cytotoxic anti-AB Ab levels. If a successful outcome were to be achieved, the initial removal of Abs was considered mandatory, and was accomplished by plasmapheresis, immunoadsorption, or a combination of both. The importance of splenectomy at the time of Tx was also stressed [12], and more intensive immunosuppressive therapy was administered than that following ABO-compatible renal Tx. For many years that was the therapeutic protocol that was followed.

More recently, substantial experience has been reported from centers in Japan, where, even today, a majority of organ Tx involves living-related donors. Use of organs from ABO-incompatible donors was, and often remains, the only available option. Recent reports involving relatively large numbers of patients have addressed the problem of Abs [32, 33]. Pre-Tx removal of Abs, which in Japan has often been carried out by means of double filtration plasmapheresis, appears to be crucial, and patients who showed an early return of Abs generally experienced humoral rejection. As reported by Ishida et al., patients who exhibited high pre-Tx IgG titers (> 1:32) had worse outcome and higher graft loss rates than patients with lower titers, despite the same aggressive pre-Tx and post-Tx treatment. ABO-incompatible kidney Tx should, therefore, be considered most carefully in this subgroup of patients [33]. However, in approximately 75% of patients, no increase in Ab titer above 1:8 (after an initial decrease to 1:4) occurred after Tx, which was associated with good long-term survival [32]. In contrast, no definite correlation between the levels of Abs and rejection episodes was seen by Aikawa et al. [34]. Although Ab levels rose during a rejection episode, high post-Tx levels were also observed in some patients who did not experience rejection. Once the initial phase of approximately 2 months has been overcome, the long-term survival (> 4 years) of a functioning ABO-incompatible kidney graft seems not to differ from that of a compatible graft [34].

Reports on ABO-incompatible kidney Tx in children are limited [35, 36, 37, 38, 39]. The initial period of concern, however, would seem to be shorter (2 weeks rather than 2 months) [38]. In 1995, Yamazaki et al. reported on seven pediatric patients receiving a conditioning regimen that included splenectomy, Ab immunoadsorption, and intensive immunosuppressive treatment; survival of both patients and grafts was 100%, up to the 6-year interval [39].

The value of splenectomy remains controversial. Although early reports emphasized the importance of perioperative splenectomy [40, 41], more recent data seem not to find splenectomy essential [11, 32, 33, 42]. In addition, increased infection susceptibility may be a problem after splenectomy [43]. One group has recently addressed this topic in some detail [33]. Of the patients who underwent splenectomy, 25% demonstrated a post-Tx increase in anti-AB Ab titers, which suggested that splenectomy had not been beneficial. Evidence was also provided, which suggested that the decrease in Ab titer that was seen in the remaining patients was not specifically associated with splenectomy.

Most groups administered intensified immunosuppressive therapy in the early post-Tx period, with quadruple or quintuple drug regimens, thus risking a higher incidence of opportunistic infections [44]. Quadruple therapy usually comprised cyclosporine or tacrolimus, with corticosteroids, azathioprine and antilymphocyte globulin. Tacrolimus has been reported to provide protection from rejection [45, 46], as has its combination with OKT3 [47]. Quintuple therapy has involved the addition of 15-deoxyspergualin or cyclophosphamide [44, 45, 47, 48, 49]. Others found that triple-drug therapy provided adequate protection against rejection [45], and there is no conclusive evidence that intensified immunosuppression is essential or even necessary.

A2-incompatible kidney transplantation

One subset of ABO-incompatible kidney Tx that should be considered separately is the Tx of a kidney from a donor of blood group A2 into a recipient of B or O blood type, or an A2B kidney into a B recipient. Blood type B recipients, in particular, are disadvantaged when awaiting a donor organ because of the rarity of this blood type. The first report of A2 kidney Tx in ABO-incompatible recipients appears to have been by Rydberg et al. in 1987. In this series, and in several subsequent series, A2 or A2B kidney grafts were successfully transplanted without pre-Tx depletion of anti-AB Abs or other specific treatment [50, 51, 52, 53, 54]. Their success is believed to be largely due to reduced antigen expression on the graft, resulting in relative protection from Ab-mediated injury. However, humoral rejection can occur [54, 55, 56, 57, 58]. For example, Brynger et al. reported that over 50% of patients with pre-Tx titers of > 1:8 can experience early non-function. It would appear that splenectomy can be omitted as part of the preparative regimen [57].

There have been several major reports on A2 kidney Tx. In a study of 50 patients, Nelson et al. demonstrated favorable long-term outcome up to 10 years. Only recipients with low anti-A Ab titers (< 1:4) were selected [56], but no patient underwent additional treatment in the form of Ab depletion or splenectomy. The 2-year survival was 94%. A more recent report by Nelson et al. emphasizes their preference for the use of A2 and A2B kidneys only in

patients with low anti-A Ab titers (< 1:4). These authors draw attention to the fact that low anti-A Ab titers are much more commonly found in patients of blood group B than O, making B patients more suitable candidates for receiving these donor organs if pre-Tx plasmapheresis is not to be performed [59].

Alkhunaizi et al. reported on 15 patients with anti-A1 Abs and/or anti-A2 Abs. Patients with titers of > 1:8 underwent plasmapheresis before undergoing A2 kidney Tx [60]. Survival was 93% after 1 year, which suggests that depletion of Abs may possibly be beneficial even when an A2 kidney is to be transplanted. One patient with a high titer who did not undergo plasmapheresis experienced hyperacute rejection and graft loss [60].

Liver

The liver has several anatomical and physiological properties that might impact on the outcome of ABO-incompatible Tx. It has the capability of manufacturing ABO antigens, can possibly produce blocking Abs, and its Kupffer cells may remove antigen-Ab complexes [61]. Furthermore, the liver seems to be able to resist injury induced by anti-human leukocyte antigen (anti-HLA) Abs, and prior donor–recipient cross-matching in this regard is frequently not performed [62, 63]. For these reasons, liver allografts were considered to be less susceptible to Ab-mediated rejection. However, ABO-incompatibility has been demonstrated to be a risk factor for Ab-mediated rejection, including hyperacute rejection [64]. Overall ABO-incompatible liver graft 1-year survival is 46%, compared with 72% for compatible grafts (CTS, 2001). However, the emergency nature of many ABO-incompatible liver transplantations may be a factor in the less favorable outcome and the more frequent need for re-transplantation [65, 66].

A difference in outcome between adult and pediatric ABO-incompatible liver Tx has been reported, with pediatric transplantations being more successful [63, 65]. The reasons for the more favorable outcome in children are not entirely clear [63, 66, 67, 68], but are likely to be related to lower anti-AB Ab levels [69] or to an immature complement system [70]. Thus, the major factors that contribute towards hyperacute rejection are absent or reduced during infancy. In children, therefore, pre-Tx Ab removal or additional therapy for the prevention of Ab-mediated rejection is usually not carried out [71]. The 1-year ABO-incompatible liver graft survival in children has been reported to be approximately 70% [71].

In adults, the presence of iso-agglutinins can result in early Ab-mediated rejection in 20–40% of patients [64, 72, 73]. The presence of preformed Abs is also thought to be associated with a higher incidence of hepatic artery and/or portal vein thrombosis, which has been reported to be between 25% and 50% after ABO-incompatible liver Tx [74, 75, 76] compared with < 1% after ABO-compatible Tx [75]. Injury of the bile duct system is also possibly related to Ab-mediated rejection, and the incidence of biliary complications is reported to be between 20% and 80%.

Pre-Tx plasmapheresis to reduce high levels of iso-agglutinins has been reported by several groups not to have any conclusive advantage. Post-Tx immunosuppression is usually more intensive than that administered after ABO-compatible liver Tx, with use of anti-lymphocyte polyclonal or monoclonal Abs (ATG or OKT3) and/or cyclophosphamide, but without clear benefit to the outcome. Despite these therapeutic manipulations, 1-year graft survival in adult recipients is very significantly reduced at only 20–40%. As re-transplantation can sometimes be carried out successfully with an ABO-compatible graft, patient survival is > 50% [76].

In an important recent study, Egawa et al. have collected data on their experience with 68 ABO-incompatible living-related liver transplantations (H. Egawa, personal communication). All patients underwent pre-Tx antibody depletion by plasmapheresis or exchange transfusion. The overall 5-year patient survival was 58%, compared with 80% after ABO-identical Tx. Analysis of outcome in various age groups showed that 5-year survival in patients < 1, 1–16, and > 16 years-old was 77%, 50%, and 22%, respectively. The incidence of intra-hepatic biliary complications and hepatic necrosis was significantly higher in adults. Predictive risk factors for increased morbidity and mortality were: age of 1 year or greater and elevated anti-ABO Ab titers before Tx. Only recipients under 1 year old presented with low pre-Tx and post-Tx anti-ABO Ab titers. Recipients ≥1 year old had either high pre-Tx anti-AB Ab titers or significantly increased post-Tx titers. All long-term survivors demonstrated low levels of IgG. Various induction and immunosuppressive regimens were used, including OKT3 or cyclophosphamide. In adults, no specific therapy presented any clear improvement in terms of graft or patient survival. This study confirmed that ABO-incompatible liver Tx can be carried out safely in infants, but highlighted the significantly increased risks and poor outcome for older patients.

As with A2-incompatible kidney Tx, Fishbein et al. demonstrated that A2-incompatible livers can probably be safely transplanted into O patients regardless of their Ab status and without prior Ab removal or intensified immunosuppressive treatment [67].

ABO-non-identical, but compatible, liver transplantation

In ABO-non-identical, but compatible, liver Tx (e.g., donor O to A, B, or AB recipient), graft-derived iso-agglutinin production can occur, as after minor ABO

-incompatible BM Tx [69]. This Ab production may result in hemolysis between post-Tx days 7–14, is usually mild or moderate, and self-limiting, but can on occasion be severe [69]. Treatment comprises aggressive intravenous hydration, diuretic therapy to maintain urine output, and plasmapheresis to remove iso-agglutinins if severe hemolysis is present. Since hemolysis results from circulating Abs directed against recipient AB antigens, it is recommended that blood transfusions, if required, be with washed RBCs of the donor ABO type.

Heart

Experience with ABO-incompatibility in clinical heart Tx is limited to very small studies and case reports [10, 77]. In most cases, the crossing of the ABO barrier was not planned but was undertaken as an emergency or was because of an error in donor ABO typing or miscommunication of donor blood type to the recipient center. In 1990, hyperacute rejection or early graft failure was reported to have developed in approximately two-thirds of adults who had undergone this procedure [78]. By 2001, the results had improved, and CTS data indicate a 54% 1-year survival, compared with 79% for compatible grafts. There is no conclusive clinical evidence that pre-Tx and/or post-Tx plasmapheresis or specific Ab adsorption is beneficial, although this is presumed to be so from experience in clinical kidney Tx and from limited experimental work. In view of the high incidence of early graft failure, ABO-incompatible heart Tx in adults should be avoided.

The situation in infants, however, may be more optimistic. Newborn infants do not produce isohemagglutinins until several months after birth. In a recent important report, West et al. reported their experience with ABO-incompatible cardiac Tx in ten infants aged 4 h to 14 months (median 2 months) [79]. Plasma exchange was performed only during cardiopulmonary bypass and standard immunosuppressive therapy was given post-Tx. No hyperacute rejection was seen. The overall patient survival was 80%, with a follow-up of 11 months to 4 years. The two early deaths were apparently from causes unrelated to ABO-incompatibility, although mild humoral (and cellular) rejection was evident in one of these two hearts at autopsy. This observation was made in one of the only two infants who had Abs to antigens of the donor blood type before Tx. Two long-term surviving children developed Abs to antigens of the donor blood group, although their titers have remained low and no damage to the graft has occurred, which suggests that accommodation may have developed.

In the remaining survivors, no Abs have developed, which suggests the possibility of the development of partial B-cell tolerance induced by exposure to donor antigens during the maturation of the immune system. In contrast, the production of Abs to A or B antigens not expressed in either donor or recipient has proceeded as in recipients with ABO-compatible donors, which suggests that deficient production of Abs to graft antigens is not due to immunosuppressive therapy. Furthermore, the absence of detectable anti-donor blood type Abs in the serum was not associated with its adsorption on to the graft, since no immunoglobulin (or complement) deposition has been detected on the grafts. The implication that T cell-independent B-cell tolerance may have developed is an important one, and cautiously encourages ABO-incompatible heart Tx in infants before they develop anti-AB Abs.

One successful experience with an A2 donor has been reported, without evidence for rejection [80], which again suggests that the low antigenicity of A2 organs is an advantage, though this remains inconclusive. Experimental ABO-incompatible cardiac Tx has been reported in non-human primates [81, 82]. In contrast to humans, Ab-mediated rejection occurred in only approximately one-third of ABO-incompatible transplantations, rather than in two-thirds. This may be related to lower antigen expression and/or lower Ab titers in the baboon. In concordant cardiac xenoTx (African green monkey-to-baboon), ABO-incompatibility added slightly to the Ab-mediated response inherent in such xenoTx [83]. In discordant xenoTx (pig-to-baboon), ABO-incompatibility was not thought to play a significant role [82, 84].

Lung/heart–lung

ABO-incompatible single-lung and heart-lung Tx have been reported [85, 86]. In both cases, Tx was performed involuntarily and occurred due to clerical errors. In the first report [85], a 67-year-old blood type B patient with idiopathic pulmonary fibrosis received a left single-lung allograft from a blood type A donor. Cyclophosphamide was added to immunosuppression with anti-thymocyte globulin induction, cyclosporine, mycophenolate mofetil, and prednisone. When increasing anti-A antibody titers were detected, antigen-specific immunoadsorption, anti-CD20 monoclonal antibody, and recombinant soluble complement receptor type 1 (TP10) were administered. The patient survived and was doing well 3 years after Tx. In the second case [86], a 17-year-old blood type O patient received a heart-lung Tx from a blood type A donor. Hyperacute rejection developed and despite emergency retransplantation, the recipient died.

The effects of minor ABO-mismatched lung Tx have also been reported [87]. Graft-derived anti-AB Ab production (as can occur after ABO-incompatible BM and liver Tx) has resulted in hemolytic anemia in some cases. Salerno et al. reported on a small group of patients after minor ABO-mismatched lung Tx (e.g., O with A), with the development of Abs directed against the host AB

antigens [87]. The source of Abs is presumably from B cells and plasma cells in the peri-bronchial lymph nodes transferred with the graft.

Bone marrow transplantation across the ABO barrier

BM or peripheral blood stem cell alloTx has become a major therapy for patients with various hematological diseases. One unique characteristic that distinguishes BM Tx from the Tx of a vascularized organ is that a large number of immunocompetent cells are transplanted from the donor to the recipient. Depending on the extent of obliteration of the host's immune system, donor cells can immunologically react against the host, sometimes resulting in graft-versus-host disease (GVHD).

Although ABO-compatibility between donor and recipient is preferred, it is often not possible. Under certain circumstances, e.g., when the donor is completely matched to the recipient for other major Tx antigens (i.e., HLAs), the risk of transplanting ABO-incompatible BM may be considered unavoidable. Major ABO-incompatibility is present when the recipient has Abs against the donor-type cells (e.g., A or B donor to O recipient; AB donor to B recipient). Minor ABO-incompatibility is present when the donor has Abs that are capable of lysing recipient cells (e.g., B donor to AB recipient). Bi-directional ABO-incompatibility is present when both iso-agglutinins and iso-antigens are incompatible between donor and recipient (e.g., A donor to B recipient; B donor to A recipient). Immuno-hematological problems may develop from any type of ABO-incompatible BM Tx.

The immediate risk of major ABO-incompatible BM Tx is hemolysis of RBCs that are contained in the graft. Therefore, major ABO-incompatible BM grafts are usually depleted of donor RBCs by various cell separation techniques [88], and clinically significant hemolysis is rare. The delayed complications of major ABO-incompatible BM Tx are hemolysis and RBC aplasia, because of persistent host iso-agglutinins that hemolyze newly formed donor erythroid cells or suppress donor RBC hematopoiesis, and occur in approximately 30% of recipients. In most patients with major ABO-incompatible BM Tx, iso-agglutinin titers directed against the donor AB type have been shown to decrease to undetectable levels, possibly due to tolerization of the host B and plasma cells to the donor antigens. In some patients, however, the titers were shown to persist without any adverse effect on the graft [88, 89].

Patients that receive minor ABO-incompatible grafts face the immediate risk of hemolysis of recipient RBCs due to donor Abs present in the BM inoculum. This complication is prevented by plasma depletion of the graft, and is rare. The delayed risk is hemolysis of recipient RBCs mediated by Abs produced by donor lymphocytes contained in the graft. This delayed hemolysis generally occurs approximately 7–14 days after BM Tx, is usually self-limiting and benign, and its incidence may relate to the post-Tx immunosuppression used to suppress GVHD. In cases of bi-directional ABO-incompatible BM Tx, the risks of major and minor incompatibility are combined.

The outcome after ABO-incompatible BM Tx varies from series to series. In the initial reports by Buckner et al. [90, and Bensinger et al. 91], the outcome of minor and major ABO-incompatible Tx was shown not to be significantly different from that of ABO-compatible Tx. It was even reported that, in a subgroup of patients with chronic myeloid leukemia, the outcome was improved [92]. In more recent reports, the outcome after major and, particularly, bi-directional ABO-incompatible BM Tx has been shown to be decreased in some groups of patients, i.e., those with acute myeloid leukemia or myelodysplastic syndromes [93, 94]. Graft failure has been reported to be associated with very high Ab titers either against donor A and/or B antigens or against the A and/or B glycosyltransferases, which mediate antigen synthesis [95, 96]. In a recent report, outcome after minor and major ABO-incompatible BM Tx was not different from ABO-compatible BM Tx with 1-year survival of approximately 70%; however, survival of bi-directional ABO-incompatible BM Tx was only 30% [97].

Major ABO-incompatible hematopoietic stem cell Tx has recently been performed via a low-intensity non-myelo-ablative conditioning regimen with the aim of inducing mixed hematopoietic cell chimerism to create a graft-versus-tumor effect [98]. Pure red cell aplasia occurred more frequently, and donor red cell chimerism was significantly delayed, than in patients receiving a standard myelo-ablative regimen. These hematological problems were associated with prolonged persistence of anti-donor isohemagglutinins, which indicated that residual host hematopoiesis represents an immunological barrier to donor hematopoietic cell engraftment.

Comment

ABO-incompatible organ Tx would appear likely to be successful when there is either low expression of antigen on the graft, as exemplified by an A2 organ, or when there is a naturally low level of Abs in the recipient, as exemplified particularly in infants and young children. Failing this, the evidence would strongly suggest that depletion of Abs before Tx is advantageous, although this does not guarantee a successful outcome, particularly in adults where the results remain significantly worse than after ABO-compatible Tx. Recent reports underline the importance of the avoidance of high initial

Ab levels, particularly of IgG, in the potential recipient, since these appear to correlate positively with graft loss. The need for intensified immunosuppressive therapy is inconclusive, but is likely to be beneficial by suppressing both T-cell help to B cells and B-cell function, and, therefore, possibly reducing Ab production. Splenectomy would appear not to be essential. Treatment of a rejection episode should aim at depletion of Abs as well as intensified immunosuppression to suppress B-cell and T-cell function. If early (< 30 days) humoral rejection can be prevented or reversed by these measures, long-lasting survival of the graft is likely.

The mechanisms by which an ABO-incompatible allograft is protected from the injurious effect of specific Ab remain poorly understood. The absence of measurable anti-A/B Abs in some patients, particularly after liver and heart Tx in infants, suggests that B-cell tolerance may have been achieved [79]. In many other patients, including adults, accommodation has been clearly documented. If B-cell tolerance or accommodation can be achieved after the Tx of an ABO-incompatible organ, the question has been asked as to why these goals have proved elusive following pig-to-primate xenoTx. There are, however, many differences with discordant xenoTx, such as higher expression of donor antigen, higher natural levels of anti-pig Ab, and reduced protection from the injurious effects of human complement provided by pig complement regulatory proteins, that makes this barrier significantly greater.

Although the results of organ alloTx across the ABO barrier are slowly improving, they still remain significantly inferior to those of Tx between ABO-compatible donor–recipient pairs. The barrier is clearly not insuperable, but it remains a difficult one to be overcome, and success is far from uniform. It should be undertaken only with caution and good reason or in situations of extreme urgency. In contrast, BM Tx across the ABO barrier would now appear to be an accepted procedure, when necessary, and, despite some potential complications, to be followed by an outcome comparable with that of ABO-compatible BM Tx.

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