

Role of Transfusion Services in Organ and Tissue Transplantation

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Introduction

Almost two decades after the introduction of modern methods of immunosuppression, transplantation of organs and tissues has become an established specialty. The theories in regard to the transfusion support needed by these patients have also matured a lot. In early eighties patients had been heavily transfused before undergoing liver or kidney transplantation, and thus were exposed to attendant risks and complications of alloimmunization to red cells and Human Leucocyte Antigens (HLA). Kidney transplant candidates received elective immunomodulatory red cell transfusions to improve graft survival. The advent of cyclosporin made this advantage marginal at best. Few programmes now use elective pre-transplant transfusions to improve graft survival. Nowadays most of the patients with chronic renal failure are given erythropoietin to avoid transfusion. Patient with end staged liver diseases have been treated by drug octreotide, variceal banding, sclerotherapy, transjugular intrahepatic portosystemic shunt placements to relieve the effects of portal hypertension in order to have less gastrointestinal bleeding and to avoid transfusion (1). This review will summarize the current concepts regarding the role of transfusion services in potential organ or tissue transplant recipients.

Hospital Transfusion Services play a great role in clinical transplantation programme. Close communication with transplant surgeons and other professional involved in the program is essential.

Morbidity, mortality and graft survival can be measured against the transfusion of blood components prior to, during, and after transplantation.

Information of special importance to blood transfusion services could include

1. History of previous pregnancy, transfusion or transplantation.
2. Laboratory tests e.g., ABO Grouping, Rh typing, direct antiglobulin test (AGT), red cell antibody screening and test for cytomegalo virus (CMV).
3. HLA typing and HLA antibodies studies are routine for organ and bone marrow recipients. Additional tests might include subgrouping of those patients who are of A or AB blood group, and an antibody detection tests in the recipients using enzyme treated red cells. Phenotyping of red cells of the donor and patient may be performed in order to follow the engraftment of transfused bone marrow.

ABO Grouping :- ABO Antigens constitute very strong histocompatibility antigens and thus they are of major importance in transplantation. Since these antigens are expressed on vascular endothelium, ABO mismatch can cause rapid graft rejection due to endothelial damage by ABO alloantibody and subsequent wide spread thrombosis with the graft. Therefore, ABO matching is very important in the transplantation of the organs that are cellular and have good blood supply i.e. kidney, heart, liver and pancreas.

Renal Transplant

Once the policy of avoidance of transfusion has been replaced by the programmes of intentional transfusions.

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This in turn, has been associated with significant improvement in the outcome of most of the transplants but not in all. In 1970's intentional pretransplant blood transfusion protocol started and data accumulated all over the world supported the thesis of Opezl et al - pretransplant blood transfusion enhanced renal allograft survival (2). Even the advent of immunosuppressive drug cyclosporine has not altered the recommendation for pretransplant transfusion. Although there seems to be some lessening of the benefits of transfusion in cyclosporin treated patients.

The way in which transfusion enhances transplant survival is unknown, but several mechanisms have been postulated e.g.

1. Pretransplant transfusion may result in early immunization of some persons to selected HLA antigens, thereby enabling the pretransplantation crossmatch to detect those cases where rejection of donor organ would be most likely to occur. Preformed HLA antibody as manifested by incompatible crossmatch is a major contraindication to transplantation, and about 30% of cases who receive pretransplant transfusions become highly immunized to HLA. This complication of pretransplant transfusion may, in fact be beneficial by preventing an unsuccessful transplant.

2. The beneficial effect of transfusion is related to the immunosuppression induced by transfusion. Perhaps through the enhancement of suppressor T cell activity, other possibilities include induction of immune tolerance by some unknown mechanism, stimulation of anti idiotypic antibody production and, then while they are actively proliferating, and destroy them by immunosuppressive drugs.

It is not clear which component of the transfused blood is responsible for more beneficial effect. Although leukocyte poor red cells, and frozen deglycerolized red cells are assumed to have low incidence of HLA immunization (3-4). Also the incidence of alloimmunization seems to be low when stored units, rather fresh units of blood are used for transfusion (5).

CMV infection, a major cause of morbidity and mortality in patients who have had renal transplant seems to be related to the presence of CMV in donor kidney.

There is no evidence to incriminate blood or blood products as the source and no need to provide CMV negative components for kidney transplant recipients. Survival of kidney graft from living related donors is enhanced by the pregraft conditioning of the recipient with several transfusions, their volume, and which portion of blood is beneficial are not established, but one protocol uses three aliquots from a single donation, given at 2-3 weeks intervals before transplantation (6). This is used by draining one unit of blood from the donor, preparing red blood cells from it, and separating the red cell unit into three aliquots using a double or triple bag. Each of them can be used for up to 42 days. Although numerous other protocols exist, until recently most transfusion services transfuse at least 5 units of blood to all new dialysis patients awaiting renal transplant (7). These were usually given in the form of white blood cells (WBC), however Red blood cells (RBC), deglycerolized RBC's and buffy coats are effective alternatives to whole blood. Preoperative blood transfusion at the time of surgery is usually not effective. It should be given at least 3 to 6 months prior to transplant (8).

At times it may be advisable to give donor specific transfusions from Rhesus D positive donor to Rhesus D negative recipient. Separating red cells from Buffy coat by using hydroxyethyl starch (HES) can do this. However, some red cells still remain present in the Buffy coat and are quite enough to immunize the recipient. A full dose of (i.e., 350-mg) of Rh immune globulin (RhIG) should be given to the recipient for the entire course of transfusion (9). When O group individuals' kidney is transplanted into a non-O group individual, it is possible that "Passenger Lymphocytes" present in the kidney at the time of transplant can become engrafted into the immunocompromized recipient. If these lymphocytes are programmed to produce anti A or anti B, then at times they can produce ABO antibodies directed against the recipients erythrocytes, these complications are marked by a positive direct AGT test and hemolytic anemia (10). Where as when two Rhesus D positive patients were transplanted from previously immunized Rhesus D negative donors, have shown temporary

Rhesus D immunization and hemolytic anemia (11).

Liver Transplant

Liver transplant programmes demand the maximum support in terms of preparedness, supply and responsiveness. Institutions that begin the liver transplant programme must make a major commitment to this support. Co-operations between the hospital administration, staff of the operating room, intensive care unit, respiratory therapy, radiology, gastroenterology, anesthesiology, coagulation laboratory and transfusion services. Most of the liver transplant centers currently use a medium of 12 units of allogenic red cells, 15-20 units of fresh frozen plasma (FFP), 2 doses of platelets (1 dose of platelet=6 units of platelet concentrates (PC) or 1 unit of apheresis platelet concentrate (APC)), 8 units of cryoppt. Children may require half of these amounts (12,13)

The medium ranges of blood and components used in liver transplant are shown in table (1&2).

Red cell salvage should aggressively be employed, transfusion services and hemostasis laboratory should be involved in monitoring hemostasis, including thromboelectrography to detect fibrinolysis (14). Liver

transplant patients usually have pre-existing anatomic problems such as severe portal hypertension and abdominal adhesions, or they develop hemodynamic instability, shock, exacerbation of coagulopathy (15).

Cardiac Transplant

Transfusion support of cardiac transplant is similar to that of open-heart surgery in which cardiopulmonary bypass is employed.

Postoperative needs vary according to individual's clinical circumstances, but for the typical organ transplant recipient postoperative transfusion are not needed.

Pancreatic Transplant

Pancreatic transfusions do not require any transfusion support. However either a type and screening of complete crossmatching of few RBC units should be established as a routine.

Bone Marrow Transplant

Patients undergoing bone marrow transplant often require prolonged blood component support. This is because there is complete ablation of their own marrow before transplantation and a relatively long period before the engrafted marrow begins to function. In addition they are prone to develop graft versus host disease and CMV infection, and all the blood products must be

Table 1. Examples of routine preoperative surgical blood orders for organ transplantation*

Components	Living donor Nephropathy	Number of units				
		Kidney	Heart	Pancreas	bone marrow	Liver
RBC	0#-2	0#-2	5-10	0#-4	0	20
PC	0	0	8	0	0	20
FFP	0	0	2	0	0	20

* Preoperative needs vary according to individual clinical circumstances, but for the typical organ recipient, postoperative blood components are not except bone marrow and liver transplant.

type and screen or no blood orders.

Table 2. Examples of units of blood components transfused in adult liver transplant patients. (12-13)

Components	Number of units, medium (range in parentheses)		
	Intraoperative	Postoperative	Total
RBC	12(1-202)	4(0-75)	19(3-211)
FFP	12(0-189)	14(0-123)	24(0-201)
PC	15(0-70)	15(0-420)	25(0-449)
Cryo.	8(0-119)	1(0-180)	8(0-290)

selected or proceeded with that in mind. For many, the period before transplantation is equally critical, since blood component therapy must be managed to minimize alloimmunization, which may later bring about rejection of the transplant and finally the marrow to be infused must be selected or proceeded to avoid immunological complications. This means removal of T lymphocytes from the marrow before its infusion and at times, extensive treatment of the recipient to remove or neutralize anti A or anti B before transplantation of an A or B incompatible marrow.

Successful bone marrow transplant demands a complete, dedicated, and well-trained staff. Institutions without such facilities cannot expect to establish successful programmes.

Pretransplant management

Presently marrow transplantation is done mostly for patients with aplastic anemia or acute leukemia, although the number of experimental or quasi-experimental transplants done for other diseases continues to rise. HLA compatibility is an important consideration. Hence the first requirement for a potential marrow transplant candidate is complete and accurate HLA typing. This should be done early in the disease and if at all possible before transfusion therapy.

Homologous bone marrow transplant

Transfusions before the homologous bone marrow transplant are known to be detrimental since they compromise the success of engraftment, particularly in patients with aplastic anemia or leukemia, transfusion are often necessary. Family members in particular should be avoided as blood donors prior to transplant since one of them may be used as bone marrow donor. This is most important to patients with hypoplastic anemia and is of less importance to patients with leukemia where graft rejection is infrequent following bone marrow transplant (16). The recipient must receive transfusion support until engraftment occurs and blood cell production becomes adequate, RBC's are usually given to maintain the hemoglobin (Hb.) at 9-10 gm/dl. This usually requires 6-20 units in 10 weeks of post transplant period. All blood components (except buffy coats from the donor) must be

irradiated (1500-5000 rad) to prevent graft versus host disease (GVHD) and be anti CMV-negative (CMV -ve) if the recipient and donor are CMV-ve. Platelet support may also be needed for bone marrow transplant recipients. HLA identical or haploidentical family members are the ideal donors for the preparation of apheresis platelets, but this is not always possible and random donor platelets are often used. These platelet transfusion may be continued every 2-4 days to maintain the platelet count in the recipient above $10-20 \times 10^9/l$. If the patient becomes refractory to platelet transfusion, therapy with HLA-matched platelets becomes more important but is not always beneficial. Some centers give granulocyte transfusions prophylactically, which most centers today give only when antibiotic resistant bacterial infection develops. Since an HLA-identical donor is usually required for bone marrow transplant, this donor (usually a sibling) may not have the same ABO and/or Rh-D type as the patient. ABO and Rh-D identity or compatibility between the donor and the recipient are not required for the success of bone marrow transplant, but incompatibilities may pose special problems for transfusion services.

Major ABO incompatibility

If the donor is group A and recipient is group O (ABO incompatibilities) then the group A red cells of the donor in aspirated marrow would be rapidly hemolysed in the recipient due to recipient anti A. This problem can be solved by processing the aspirated marrow to delete contaminated red cells (17). Fortunately stem cells do not express A and B antigens. The group O recipient transplanted with group A marrow may continue to produce anti A and anti B for 3-4 months or in rare cases for 10-20 months post transplant. The grafted marrow will begin to produce a new population of blood cells. Group A red cells will appear in the circulation when the recipient anti A disappears.

Hemolysis of the newly produced group A red cells may be noted about 2 months post transplant. This may last for approximately 3 weeks and may result in temporary drop in patient's Hb. If transfusions are necessary, washed group O RBC's can be given, these components should be CMV-ve if the patients has been determined as CMV-ve.

In addition all blood components transferred to BMT recipients should be irradiated to prevent graft versus host

disease, circulating donor WBC's are usually found about 2½ weeks post BMT and platelets follow about 4 weeks post BMT.

Minor side ABO incompatibility

When marrow from a group O donor is transfused into a non-group O recipient (A, B, AB), the plasma should always be removed in order to reduce incompatible alloantibodies given to the recipient. However, in almost 10-15% of such BMT's, there is rather abrupt onset of immune hemolysis, which begins about 7-8 days post transplant and may last for 2 weeks. The direct AGT is positive, anti A or anti B can be recovered in elutes and the hemolysis may result in hemoglobinemia and hemoglobinuria. An additional 30% of such BMT recipient may develop a positive AGT but does not manifest gross hemolysis. This phenomenon is due to "passenger B lymphocytes" in the bone marrow that is producing alloantibodies. This hemolysis is transient but may persist for up to 2 weeks and may require transfusion. Irradiated group O washed cells, CMV-ve if the recipient is CMV-ve, would be the component of choice.

This same phenomenon may develop following solid organ transplants of kidney, liver, lungs, pancreas and spleen. Typically there is an abrupt onset during the first 2-3 weeks post transplant. Although usually transient, the hemolysis may continue for up to six months.

Chimerism

In spite of intensive pretransplant chemotherapy and irradiation, some of the host hemopoietic cells may survive and subsequently coexist with the transplanted donor cells. This results, what has been termed mixed hemopoietic chimerism and thus the recipient may have a dual cell population. This phenomenon does not mean that the recipient will necessarily have a recurrence of the hemolytic malignancy.

Discussion

Although the organ or tissue transplants have become a routine in many good centers around the globe, the transfusion support will continue to play an important role. The story of organ transplant and transfusion services has had many twists and turns. For example the purpose of kidney transplantation has moved from avoidance to white

cell depletion, to deliberate transfusion, to current view of avoidance again.

In lung transplantation, the use of single lung replacement or sequential bilateral replacement, improves the outcome and reduces the need for cardiopulmonary bypass and transfusion in comparison to traditional heart-lung replacement (18).

Transfusion support in intestinal transplantation in one center used 11 units of red cells in its first few cases (19) where as some centers give cadaver donor blood to intestinal transplant recipients (20). This concept of creating donor microchimerisms via blood or bone marrow, to induce tolerance is also under investigation in liver, kidney and heart transplantation (21).

Transplant patients have also been benefitted from experiences gained over the years. Improved perfusion solutions like diasparine crosslinked hemoblobulin (DCL-Hb.), is an alternative to conventional crystalloid or colloid intravenous solutions and its major application is to treat surgical and trauma patients to supplement or to eliminate the need for blood transfusions and to improve the tissue perfusion (22).

Greater surgical experience with procedures also lead poorly functional organs and fewer re-operations for bleeding in the immediate post-transplant period. Better hemostasis of large bleeding surfaces can be obtained by the use of the organ laser. The drug aprotinin, which is a 6500-Kda-serine protease inhibitor, derived from bovine pancreas has number of substrates. In decreasing potency it inhibits plasmin, plasma kallikrein, APC(activated protein complex - factor XIa, factor Va and tissue factor complex) two chain urokinase, factor Xa and thrombin. Aprotinin significantly prolongs activated thromboplastin time (APPT) but not prothrombin time (PT), most probably as a result of its effect on IXa and plasma kallikrein. Since kallikrein is not associated with bleeding and factor XI deficiency is considered a mild bleeding disorder, these combined data suggest that aprotinin is a better inhibitor of fibrinolytic pathways than of thrombin formation (23-26).

Aprotinin is licensed in United States for reducing blood use in cardiac surgery. However, risks of thrombosis and



anaphylactic reactions have been reported. Some of thrombocytopenia in liver failure may be due to thrombopoietic deficiency and thus thrombopoietic therapy may become useful when a liver transplant is imminent (27).

To conclude, in future blood transfusion services will be called on for support of artificial organ transplant or Xenotransplant from animals. This almost 360-degree evolution, resulting from added knowledge and the development of new drugs, illustrates both past challenge and the flexibility required for the future. The lesson we learned so far will serve as critical building blocks for our transplantation colleagues' new age of advance.

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