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Graft rejection after allogeneic bone marrow transplantation: A review

*Emmanuel Ifeanyi Obeagu[1], Quratulain Babar[2] and Chukwuma J. Okafor[3]
[1]Department of Medical Laboratory science, Imo State University, Owerri, Nigeria
[2]Department of Biochemistry, Government College University, Faisalabad, Pakistan
[3]Department of Pathology and Biochemistry, State University of Zanzibar, Tanzania.
*Corresponding Author: *emmanuelobeagu@yahoo.com*

Abstract

Bone marrow transplant rejection is generally defined as lack of donor cells in patients with pancytopenia and reduced bone marrow cell counts. Chimera studies using FISH (in gender-differentiated transplants) or microsatellite methods can allow early diagnosis of GFR, which can be a crucial opportunity to optimize the chances of saving patients who have failed transplants. An allograft is a graft between members of the same species that are genetically different. This is the most common form of transplant. The degree of allograft rejection depends in part on the degree of similarity or histocompatibility between donor and recipient. The stem cells used for allogeneic transplantation come from another person, called a donor. After the patient receives chemotherapy and / or radiation therapy, the donor stem cells are administered. The immune response to transplanted organs consists of cellular and humoral mechanisms. Although other cell types are involved, T cells are crucial in transplant rejection. The rejection reaction includes the sensitization stage and the effect stage. The clinical stages of rejection include hyperacute rejection, acute rejection and chronic rejection. However, there may also be an accelerated rejection stage.

Keywords: graft rejection, allogeneic bone marrow, transplantation

Introduction

Transplant rejection

The term transplant rejection refers to the immune-mediated rejection of residual host cells against donor cells due to genetic differences between recipient and donor. Therefore, the term only relates to allograft (Lowsky and Messner 2016). Immune rejection of hematopoietic stem cell transplants is the leading cause of transplant failure (Olsson et al., 2013). Bone marrow transplant rejection is usually defined as the lack of donor cells in patients with pancytopenia and a reduced number of bone marrow cells (Martin 2016). Chimera studies through FISH methods (in sexually dysfunctional transplants) or through microsatellites allow for early diagnosis of GFR and are critical to optimizing the likelihood of rescuing patients who have failed transplants (Locatelli et al., 2014). They should be performed routinely, especially for insufficient spinal cord function and may be candidates for donor lymphocyte infusion (DLI) or a second transplant

(Martin 2016). The incidence of GFR varies with transplantation methods, studies, and reports. In autologous transplantation, a reasonable estimate of GFR is between 1% and 3%. The incidence of GFR is higher in allogeneic transplant recipients, especially if the patient receives HLA-incompatible or T-cell depleted grafts or single-unit CB transplants (Lowsky and Messner 2016). Olsen et al. (2013) reported a large retrospective study. The overall GFR rate for 967 transplant operations performed between 1995 and 2010 was 5.6%. The incidence of GFR in SCT recipients was higher to maintain effective hematopoietic function in the long term; The production of red blood cells, white blood cells, and platelets, and their release into peripheral blood (Locatelli et al., 2014). Graft is the most important variable for better overall survival after stem cell transplantation (Cluzeau et al., 2016).

Allogeneic transplantation

Allogeneic transplantation of stem cells comes from another person, called a donor. After the patient receives chemotherapy and/or radiation therapy, donor stem cells are provided to the patient. This is also called ALLO transplantation.
Many people experience an "anti-graft cancer effect" during ALLO transplantation. This is when the new stem cells recognize and destroy cancer cells that are still in the body. This is the main ALLO transplant method for treating cancer.
Finding a "compatible donor" is a necessary step in ALLO transplantation. The matched donor is a healthy donor whose blood protein (called human leukocyte antigen (HLA)) closely resembles blood protein. This process is called HLA typing. Siblings of the same parent are usually the most compatible, but another family member or an unrelated volunteer may also be compatible. If your donor's protein closely resembles yours, you are less likely to experience a serious side effect called graft-versus-host disease (GVHD). In this case, the healthy transplanted cells will attack your cells.

Allogeneic grafts are grafts between members of the same species that are genetically different. This is the most common form of transplantation.

The degree of rejection of an allograft partly depends on the degree of similarity or histocompatibility between the donor and the recipient. (Baldwin et al., 2016.)

The degree and type of response also vary by transplant type. Certain parts, such as the eyes and brain, have an immunological advantage (that is, they have few or no immune system cells, and can even tolerate mismatched grafts). The skin graft is initially not vascularized, so it will not show rejection until the blood supply develops. The heart, kidney, and liver are highly vascularized organs, and transplantation will elicit a strong cell-mediated response in the host.

Bone marrow transplant

HLA writing is also very important in bone marrow transplantation. This type of graft should avoid both the rejection of the transplant tissue and the damage of the host tissue due to the transplant lymphocyte, and damage the tissue host by the transplanted lymphocytes (the second half of this chapter). Therefore, the recipient organism is usually a preferred donor, a preferred donor, and is the same twin, HLA identical brother or the relative relative bidirectional bidirectional bidirectional.

B. Confirming that the cytotoxic antibody in the serum of the recipients directed against the lymphocytes of the recipient can be of the signal that the recipient is already immunized with possible donors. This is achieved through a test called CrossMatch. The recipient's serum is tested against the lymphocytes of the possible donors and the phenotype cell panels known. This test is useful to prevent rapid rejection of tissues or transplanted organs.

C. Mixed cross-based crops can be used to avoid Grafter cost reactions, and can still cause Heydin Parsinks due to the incompatibility of the indefinite antigenic system. Cultures are established by mixing receptor lymphocytes from potential donors with lymphocytes. Several pairs of donor recipients must minimize each other in these cultures. The antigens that cause gennestically different tissue rejections are called

histocompatible antigens. They are histocompatible gene products. The tissue compatible antigens are encoded by more than 40 loci, but the cause of the most active allograft rejection is in the main histocompatibility complex (MHC).

In humans, MHC is called human leukocyte antigen system (HLA) and is on chromosome 6 on the short arm near the complement gene. Other antigens can only cause weak responses, but some mild antigens can lead to strong rejection responses. The MHC gene is expressed mainly CO, which means that each individual expresses these genes of both alleles on the cell surface. In addition, they are inherited as haplotypes or two hundred sets (one of each parent). This makes half half of their parents for MHC complexes. This also results in a possibility of 25% that individuals can have a brother with HLA itself.

Gene HLA Human Three Class I Main Alleles (Hlaa, B, C), and three main class II alleles (Hladr, DQ, DP). HLA polymorphisms, especially the Loci of Hlaa, B and DR are important biological barriers for successful transplants. As the graft is recognized and rejected closely, HLA imbalances have an important effect on the extension of graft survival (Shi X et al., 2017).

MHC molecules are divided into two classes. Class I molecules are generally expressed in all nuclease cells, while class II molecules are expressed only in specialized antigen metaphisema cells (APC), such as dendritic cells, activated macrophages and B cells. Physiological function Of the MHC molecules is to present antigenic peptides to T cells to recognize antigens only when t lymphocytes are presented to MHC molecules and complexes. Class I molecules participate in the presentation of antigenic peptides of intracellular peptides (eg, intracellular virus, tumor antigen, ceramingen) to CD8 T cells. Class II molecules are present in CD4 T cells, such as extracellular cells. Rejection Mechanism.

The immune response to the transplanted organs consists of cellular mechanisms (mediators of lymphocytes) and body type type (antibody mediated by the antibody). Other types of cells are also involved, but T cells are fundamental in the rejection of grafts. The elimination reaction consists of a raising stage and effector stage. At this stage, T cells CD4 and CD8 through the cells of the foreign graft are recognized through these Tcell receptors. The recognition of antigen requires two signals. Initially, it is provided by the interaction of the T cell receptor with the antigen presented by the MHC molecule by the interaction with the second antigen by the interaction of the receptor / ligand of the CO stimulation on the surface T Cell / APC. Of a large number of co-timulation pathways, the interaction between CD28 on the surface of the T cell and its APC surface ligand, B71 or B72 (known as CD80 or CD86 respectively) has been studied more. (Clarkson et al., 2005). In addition, the associated antigen of cytotoxic T lymphocyte 4 (CTLA4) is also attached to these ligands and provides an inhibition signal. Other coestimulating molecules include CD40 and their CD40L ligand (CD154).

Normally, the helix of the MHC molecule forms a peptide binding groove and is occupied by peptides from normal cell proteins. Thymus or central tolerance mechanisms (clone deletion) and peripheral tolerance mechanisms ensure that these complex MHC self-peptides are not recognized by T cells, thereby preventing autoimmune reactions.

There are at least two different but not necessarily mutually exclusive ways of foreign body recognition: direct and indirect. Each will result in a different set of allogeneic specific T cell clones.

Direct pathway

In the direct pathway, the host T cell recognizes the donor or stimulates the complete aloMHC molecule on the cell surface. Mechanically, the host T cell treats the allogeneic MHC + homologous peptide molecule in the same form as the exogenous MHC + peptide itself, and therefore recognizes the donor tissue as a foreign tissue. This pathway may be the main way to participate in the early alloimmune response.

Transplanted organs carry varying amounts of transient APC in the form of interstitial dendritic cells. This APC has a high density of alloMHC molecules that can directly stimulate receptor T cells. Compared with the number of clones targeting the antigen presented by autoAPC, the relative number of T cells proliferated by contact with allogeneic cells or donor cells is very high. Therefore, this approach is very important in acute allogeneic rejection.

Indirect pathway

In the indirect pathway, T cells recognize processed allogeneic antigens presented as peptides by autoAPC. Secondary reactions, such as those that occur in chronic or late acute rejection, are related to the response of proliferative T cells to more variable components, including peptides that were previously immune-silenced. This change in the T cell response pattern is called epitope transfer or spread. The link between 's own MHC+-induced iso-peptide T cells and the development of acute vascular rejection has been shown to be mediated in part by accelerated isoantibody production. In addition, chronic allograft vascular disease may be mediated by indirectly prepared T cells.

Molecular mechanism of T cell activation

In the process of T cell activation, membrane-bound inositol phospholipids are hydrolyzed to diacylglycerol (DAG) and IP3. This will increase the cytoplasmic calcium. The increase in calcium promotes the formation of calmodulin complexes, which activate many kinases as well as protein phosphatase IIB or calcineurin. Calcineurin dephosphorylates activated T-cell nuclear factor cytoplasmic (NFAT), causing it to translocate to the nucleus, where it binds to the IL2 promoter sequence and then stimulates IL2 mRNA transcription. Many other intracellular events, including DAG activation of protein kinase C (PKC) and activation of nuclear factor kappa B (NFkB), also occur at the molecular level.

Effector stage

Antigen-dependent and independent allogeneic factors contribute to the effector mechanism. Initially, the non-immune "response to injury" (ischemia) induces a nonspecific inflammatory response. Therefore, as the expression of adhesion molecules, MHC class II, chemokines and cytokines are up-regulated, it increases the presentation of antigens to T cells. It also promotes the elimination of intact soluble MHC molecules that can activate the pathway. indirect allogeneic recognition. After activation, CD4-positive T cells initiate a macrophage-mediated delayed-type hypersensitivity (DTH) response and help B cells to produce antibodies.

Several T cells and T cell derived cytokines, such as IL2 and IFNγ, are up-regulated shortly after transplantation. Subsequently, β chemokines such as RANTES (regulated by normal T cell activation, expression and secretion), IP10 and MCP1 are expressed, promoting strong macrophage infiltration of the allograft. IL6, TNFα, inducible nitric oxide synthase (iNOS), and growth factors also play a role in this process. Growth factors, including TGFß and endothelin, can cause smooth muscle proliferation, intimal thickening, interstitial fibrosis, and glomerular sclerosis. Endothelial cells activated by macrophages and T cell-derived cytokines express MHC class II, adhesion molecules, and costimulatory molecules. These can present antigens and therefore recruit more T cells, thereby amplifying the rejection process. CD8-positive T cells mediate cell-mediated cytotoxicity by providing a "fatal blow" or inducing cell apoptosis.

Apoptosis The last common pathway of cell lysis is to trigger apoptosis in target cells (Krupnick et al., 2002). After CTL is activated, they form cytotoxic granules containing perforin and granzyme (Krupnick et al., 2002). When the target cell recognizes and docks, these particles fuse with the effector cell membrane and squeeze out the contents at the immune synapse. Through a still unknown mechanism, granzyme inserts into the cytoplasm of target cells. Granzyme B can trigger apoptosis through several different

mechanisms, including direct lysis of procaspase3 and indirect activation of procaspase9. This has been shown to play a leading role in inducing apoptosis in allograft rejection.

Alternatively, CD8-positive CTLs can also use Fas-dependent pathways to induce cell lysis and apoptosis. The Fas pathway is also important in limiting the proliferation of T cells in response to antigen stimulation. This is called cannibalism between activated CTLs. Cell-mediated cytotoxicity has been shown to play an important role in acute rather than chronic allograft rejection.

The role of natural killer cells

Natural killer (NK) cells are important in transplantation because they can distinguish between allogeneic cells and self cells, and they have a powerful cytolytic effect mechanism (Kitchens et al., 2006). These cells can produce the largest response to the effect is without any prior immune sensitization. Unlike T and B cells, NK cells are activated due to the absence of MHC molecules on the surface of the target cells (the "self-elimination" hypothesis). This recognition is mediated by various inhibitory NK receptors, which are activated by specific alleles of MHC class I antigens on the cell surface.

In addition, they have stimulatory receptors that are activated by antigens on non-self cells. These effect responses include cytokine release and direct toxicity mediated by perforin, granzyme, Fas ligand (FasL), and TNF-related apoptosis-inducing ligand (TRAIL). Through this "double negative" activation mode, they are believed to play a role in the rejection of bone marrow and transplantable lymphoma in animal models. NK cells also provide support for CD28-positive host T cells and promote allograft rejection (McNarney et al., 2006). Over the years, its importance in the field of bone marrow transplantation has been recognized. In humans, its graft-versus-host allograft reaction has been used for its effective graft anti-leukemia effect and helps to improve the sustained remission rate of patients with acute myeloid leukemia.

NK cells are now considered to be active participants in the acute and chronic rejection of solid tissue grafts (Kitchens et al., 2006). Recent studies have shown that NK cells exist and are activated after infiltration of solid organ allografts (Kitchens et al., 2006). They can regulate the outcome of cardiac allografts. Studies have also shown that people with the killer cell immunoglobulin -like receptor that is suppressed by the donor's MHC have a reduced risk of liver transplant rejection. In the case of kidney transplantation, these cells are not suppressed by current immunosuppressive protocols. The role of innate immunity.

Although T cells play a key role in acute rejection, it is now believed that upregulation of pro-inflammatory mediators in allografts occurs prior to the T cell response. This early inflammation after implantation is due to the innate response of the tissue. The injury has nothing to do with the adaptive immune system. Several recent studies have examined the role of Toll-like receptor (TLR) agonists and TLR signaling in allogeneic recognition and rejection.

These innate mechanisms by themselves do not appear to be sufficient to cause transplant rejection. However, they are important for optimal adaptive immune response to graft and may play an important role in tolerance-induced resistance. Developing methods to weaken the innate immune response, which has the potential to affect a variety of diseases and can also have a major impact on transplantation.

The clinical stage of rejection

Hyperacute rejection

In hyperacute rejection, the transplanted tissue is rejected within minutes or hours due to rapid destruction of vascularity. Hyperacute rejection is fluid-mediated because the recipient has pre-existing antibodies against the graft, which can be caused by previous blood transfusions, multiple pregnancies, transplants, or previous xenografts, and humans already have antibodies. The antigen-antibody complex activates the complement system, causing massive thrombosis in the capillaries, thus preventing the vascularization of

the graft. The kidney is more prone to hyperacute rejection; the liver is relatively resistant, probably due to its dual blood supply, but more likely due to an incomplete understanding of immunological properties.
Hyperacute rejection process (early)

1. Hyperacute rejection usually occurs within the first few hours after transplantation and is mediated by antibodies against the ABO or MHC antigen of the graft. Antibodies against other allogeneic antigens (such as vascular endothelial antigens) may also play a role in this type of rejection.

2. Once the antibody binds to the transplanted tissue, the complement system is activated, leading to chemotactic attraction of granulocytes and activation of inflammatory circuits, and/or cytotoxic antibody-mediated (ADCC) can cause rejection.

3. An important pathological feature of hyperacute rejection is the formation of a large number of intravascular platelet aggregates, leading to thrombosis, ischemia and necrosis. Platelet thrombosis may be the result of a variety of factors, including immunocompromised endothelial cells and/or activated neutrophils that release platelet activating factor (PAF).

4. Hyperacute rejection is difficult to treat and results in graft loss. Using appropriate cross-matching techniques, this type of rejection should be almost 100% avoided.

5. The main limitation of xenotransplantation (eg pig to human) is hyperacute rejection caused by all cellular antigenic antibodies produced in humans, even before any known xenogeneic tissue (natural antibodies) is exposed.

Acute rejection

Acute rejection usually occurs in the first 6 months after transplantation.

Acute rejection occurs mainly in the first days or weeks after transplantation. Up to 70% of transplant recipients will experience one or more acute rejections.

1. When it occurs on the first day after transplantation, it may correspond to a secondary immune response (the second group), which means that the patient was previously sensitive to HLA antigens present in the organ donor (due to previous transplantation , Pregnancy or blood transfusion).

2. When it occurs after the first week after transplantation, it usually corresponds to the first (main) reaction.

3. Acute rejection is mediated primarily by T lymphocytes, and the relative importance of CD8 + cytotoxic lymphocytes and CD4 + helper lymphocytes has been controversial. Most likely, both subsets play an important role.

In rejected organs, the cellular infiltration contains mainly monocytes and T lymphocytes with helper phenotype and cytotoxic phenotype, and less frequently B lymphocytes, NK cells, neutrophils, and eosinophils. All of these cells can play an important role in the rejection process. The feather CD4 + T helper cells are thought to play a key role because they release a growth factor:

i. IL2 and IL4 promote the expansion of CD8 + lymphocytes and B cells

ii. Interferon gamma enhanced the expression of MHC class II antigens in

iii grafts. Chemotactic interleukins, such as IL8 (also released by activated monocytes and macrophages), attract lymphocytes and granulocytes to the transplanted organ.

In most cases, if detected early, acute rejection can be reversed by increasing the dose of immunosuppressive agents or by temporarily using additional immunosuppressive agents. However, this simple method is complicated by the uncertainty that often exists in the diagnosis of rejection (Gabriel. 1998).

Acute cellular rejection

Acute cellular rejection is mediated by lymphocytes, which have been activated against the donor antigen, primarily in the recipient's lymphatic tissue. Donor dendritic cells (also called passenger leukocytes) enter the circulation and function as antigen presenting cells (APC).

Body fluid rejection

Body fluid rejection is a form of allograft injury and subsequent dysfunction, primarily antibody and complement mediated. It can occur immediately after transplantation (hyperacute) or within the first week. Antibodies are preformed antibodies or represent anti-donor antibodies produced after transplantation. Proteinuria is related to the detection of donor-specific antibodies, and may be an important factor in determining the rapid decline of glomerular filtration rate and early transplantation failure in patients with new HLA antibodies (Fotheringham et al., 2011).

The presence of even low levels of donor-specific antibodies that may not be detected by complement-dependent flow cytometry and cytotoxicity cross-checks has been shown to be related to poor allogeneic kidney transplantation results. (Willicombe et al., 2011). These patients may need to increase immunosuppression.

The inactive product of the classic C4d pathway has been shown to deposit in peritubular capillaries (PTC), and immune detection of this product in kidney transplant biopsy can be used to diagnose antibody-mediated rejection. However, one study showed that there are significant fluctuations in the C4d Banoff score in the first year after transplantation, which may reflect the dynamic and inert nature of the body fluid process. (Loupy et al., 2011). Therefore, C4d itself may not be a sufficiently sensitive indicator, and detection of microvascular inflammation with donor-specific antibodies may be more helpful in diagnosing body fluid rejection.

Diagnosis of acute rejection

a. The initial diagnosis is usually based on clinical suspicion. The deterioration of the function of transplanted organs is the main basis for considering the diagnosis of acute rejection. Confirmation of birds usually requires a biopsy of the transplanted organ. Histological criteria have been established for identifying acute rejection in transplanted organs. A sign of graft rejection is monocyte infiltration, which is expected in a typical delayed hypersensitivity reaction. However, mononuclear cell infiltration can sometimes be seen in transplanted organs that are obviously functioning normally (not as severe as acute rejection). Non-invasive diagnosis of rejection at degrees centigrade. Since biopsy is an invasive procedure with possible complications and defects, several non-invasive diagnostic methods of rejection have been tried. Special attention should be paid to the measurement of cytokines released by activated T lymphocytes (such as IL2) in serum and urine (in the case of kidney transplantation). However, these tests have been found to lack sensitivity and specificity (Gabriel, 1998).

Chronic rejection

Chronic rejection occurs months or years after the acute rejection subsides. Chronic rejection is mediated by antibodies and cells. The use of immunosuppressive drugs and tissue typing methods increases the survival rate of allografts in the first year, but cannot prevent chronic rejection in most cases.

Chronic rejection manifests as fibrosis and scarring in all transplanted organs, but the specific histopathology depends on the transplanted organ. In heart transplantation, chronic rejection manifests as accelerated coronary atherosclerosis. In the transplanted lung, it manifests as obliterative bronchiolitis. In liver transplantation, chronic rejection is characterized by the disappearance of the bile duct syndrome. In renal recipients, chronic rejection (called chronic allograft nephropathy) manifests as fibrosis and glomerulopathy. The following factors can increase the risk of chronic rejection:

a) Past episodes of acute rejection
b) Insufficient immunosuppression
c) Delay in initial transplant function
d) Donor related factors (eg, advanced age, hypertension)
e) Reperfusion injury To organs
f) Extended cold ischemia time
g) Container factors (eg, diabetes, hypertension, hyperlipidemia)
h) Post-transplant infection (eg, cytomegalovirus [CMV])
Delayed or chronic rejection Additional description of

Delayed or chronic rejection is characterized by the gradual loss of function of the transplanted organ. Recent data shows that there is a positive correlation between the number of HLA incompatibility and the progression of chronic rejection, which is difficult to control with any type of treatment.

1. Whether chronic rejection is a single process or represents the ultimate common pathway of multiple injuries that have occurred over a long period of time, including acute rejection episodes, infections and atherosclerosis, is still uncertain.

2. The functional impairment associated with chronic rejection appears to be due to both immune and non-immune processes.

The immune component of chronic rejection is believed to cause vascular endothelial damage. Granulocytes, monocytes, platelets, and other cells have a greater tendency to adhere to the damaged vascular endothelium. The expression of PAF in the endothelial cell membrane may be one of the main factors that determine the adhesion of neutrophils and platelets. Two types of cells have PAF receptors on their membranes.

b. Activated white blood cells release a variety of interleukins and soluble factors at the level of the damaged vessel wall, including IL1 and platelet-derived growth factor (PDGF). The damaged endothelium is covered by a layer of platelets and fibrin, and finally by fibroblasts and proliferating smooth muscle cells. Due to the inflammatory characteristics of this process, the

c. final result is a proliferative lesion in the blood vessel, which develops into fibrosis and occlusion (Gabriel. 1998).

Conclusion

Bone marrow transplant rejection is generally defined as lack of donor cells in patients with pancytopenia and reduced bone marrow cell counts. The degree of allograft rejection depends in part on the degree of similarity or histocompatibility between donor and recipient. The immune response to transplanted organs consists of cellular and humoral mechanisms. Although other cell types are involved, T cells are crucial in transplant rejection.

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