Acute Graft-versus-Host Disease: An Immunologic Perspective

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ABSTRACT

Background: Acute graft-*versus*-host disease (GVHD) following allogeneic hematopoietic stem cell transplant (AHscT) is an immune triggered process, leading to profound immune dysregulation and organ dysfunction. Three phases summarize the development of the immunopathophysiology of acute GVHD: an afferent phase, an efferent phase and an effector phase. A panel of plasma biomarkers including IL-2-receptor-a, TNF receptor-1, IL-8, and hepatocyte growth factor has been suggested as a confirmatory tool for the diagnosis of acute GVHD at the onset of clinical symptoms and to provide prognostic information independent of GVHD severity. Initial therapy for acute GVHD ranges from a simple observation or a trial of topical corticosteroids for skin GVHD of stage I or II, to systemic treatment in patients with grade II-IV acute GVHD.

Objectives: The aim of this work is to summarize the most recent available data concerning acute graft versus host disease from biology, immunopathogenesis, diagnosis and therapy.

Material and Methods: We searched the PubMed and Google scholar databases for relevant studies acute graft-versus-host disease an immunologic perspective.

Conclusion: Acute graft versus host disease (aGVHD) remains the second leading cause of death following allogeneic hematopoietic stem cell transplant (AHSCT). Over the last five years, the progress in understanding the pathophysiology of this immune based-process helped redefine graft versus host reaction and opened new possibilities for novel preventive and therapeutic approaches.

Keywords: Bone marrow transplantation, Acute versus host disease.

INTRODUCTION

Acute graft-*versus*-host disease (GVHD) following allogeneic hematopoietic stem cell transplant (AHscT) is an immune triggered process, leading to profound immune dysregulation and organ dysfunction. Despite pivotal advances, acute GVHD remains the second leading cause of death, after disease relapse, in patients undergoing AHscT [1]. Historically, acute GVHD has been defined as a manifestation of rejection occurring in the first 100 days following AHscT, while chronic GVHD referred to signs of rejection occurring after 100 days. However, a clear distinction between the two conditions has been challenged by the recognition of signs of acute GVHD and chronic GVHD outside of these delineated periods [2]. Evolution in clinical immunology brought more insight into the pathogenesis of GVHD and several components were identified to interplay in the mechanism of GVHD: a genetic component favoring the role of HLA compatibility in AHscT and immune/biologic component [3]. Risk factors for the development of acute GVHD, other than the extent of HLA disparity, include increased age of both the recipient and the donor, gender disparity, multiparous female donors, ineffective GVHD prophylaxis and the intensity of the transplant conditioning regimen and the source of graft [4]. Classically, three phases summarize the development of the immunopathophysiology of acute GVHD: an afferent phase, an efferent phase and an effector phase [5]. Clinical manifestations of acute GVHD include specific derangements in the skin, liver and gastrointestinal tract, occasionally the eyes and oral mucosa. It often presents with skin rash, diarrhea, elevated bilirubin, and it is associated with recurrent infections. Acute GVHD most commonly occurs 2 to 42 weeks after stem-cell infusion. A hyperacute form of GVHD can occur within the first 2 weeks of AHscT, and is usually due to significant HLA mismatch or inadequate GVHD prophylaxis. It can be rapidly fatal [6]. A panel of plasma biomarkers including IL-2-receptor-a, TNF receptor-1, IL-8, and hepatocyte growth factor has been suggested as a confirmatory tool for the diagnosis of acute GVHD at the onset of clinical symptoms and to provide prognostic information independent of GVHD severity [7]. There are no standardized preventive measures for acute GVHD. Prophylactic approach is based mainly on immunosuppression either by T cell depletion or pharmacologically. Immunosuppression remains the primary pharmacologic strategy to prevent GVHD. The most commonly includes a combination of a calcineurin inhibitor (cyclosporine (csa) or tacrolimus (TAc)) and a short course of methotrexate (MTX) [8]. In acute GVHD, treatment should always be tailored to the severity of the presentation and targeting the symptoms. Initial therapy for acute GVHD ranges from a simple observation or a trial of topical corticosteroids for skin in GVHD of stage I or II, to systemic treatment in patients with grade II-IV [8]. Alternative therapies for steroid refractory cases include antithymocyte globulin (ATG), cyclosporine alone, mycophenolate

mofetil, anti-iL-2 receptor, anti-cD5-specific immunotoxin, pan T-cell ricin A-chain immunotoxin, ABXcBL, etarnercept, infliximab, daclizumab, vilizumab and pentostatin. These agents can be used alone or in combination [9].

Bone marrow transplantation:
Peripheral Blood Stem Cells (PBSCs) have gained popularity as a source of stem cells since their initial introduction in the 1980s**.** The most important cell needed for successful transplantation is the hematopoietic stem cell. Currently, the major sources of stem cells for transplantation include bone marrow, peripheral blood, and cord blood. These can be obtained from various donors. When they are obtained from the recipient, they are called autologous. When they come from someone other than the recipient, they are termed allogeneic [10].

Bone marrow transplantation and hematopoietic stem cell transplantation have been used with increasing frequency to treat numerous malignant and nonmalignant diseases. Post-World War II "Cold War" fears of nuclear warfare stimulated interest in the effects of radiation on the human body [11].
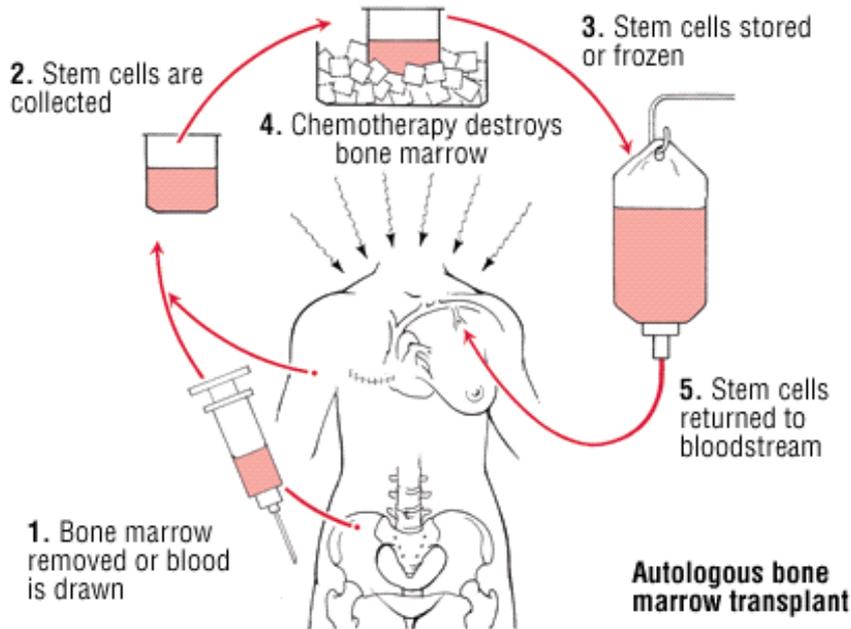

Figure (1): Autologous bone marrow transplant [10]

The 3 types of allogeneic donors are syngeneic, related, and unrelated. When the donor is an identical twin, donation is termed syngeneic. As the names imply, related allogeneic donors are relatives, and unrelated donors are identified through a donor registry or from a cord blood bank [12].
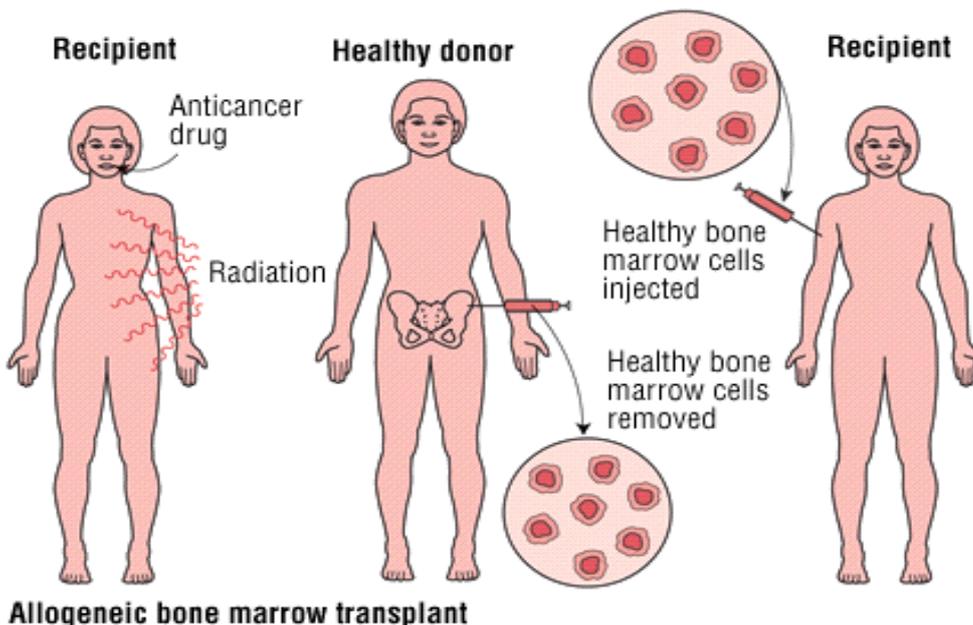

Figure (2): Allogeneic bone marrow transplant [10]

Phases of aGVHD:

Acute graft-*versus*-host disease (aGVHD) following allogeneic hematopoietic stem cell transplant (AHscT) is an immune triggered process, leading to profound immune dysregulation and organ dysfunction. Despite pivotal advances, aGVHD remains the second leading cause of death, after disease relapse, in patients undergoing AHscT [1]. **Teshima et al.** [13] emphasized the crucial role of mature T cells in the development of aGVHD. The development and evolution of acute GVHD can be conceptualized in three sequential phases (figure 3) to provide a unified perspective on the complex cellular interactions and inflammatory cascades that lead to acute GVHD: activation of the antigen presenting cells (APCs), donor T cell activation, differentiation and migration and effector phase.
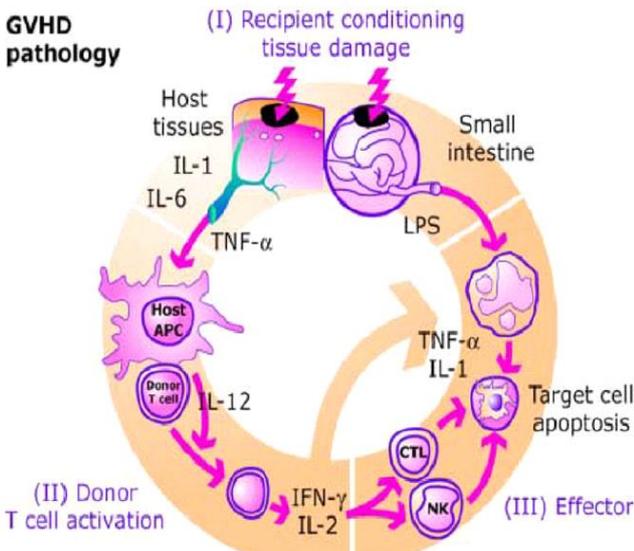

Figure (3): Three phases of GVHD immunobiology [13]

Phase 1: Activation of antigen presenting cells (APCs):

The earliest phase of acute GVHD is set into motion by the profound damage caused by the underlying disease and infections and further exacerbated by the BMT conditioning regimens (which include total body irradiation (TBI) and/or chemotherapy) that are administered even before the infusion of donor cells. This first step results in activation of the APCs. Specifically, damaged host tissues respond with multiple changes, including the secretion of proinflammatory cytokines, such as TNF-α and IL-1, described as the 'cytokine storm'[14].

Phase 2: Donor-T-cell activation, differentiation and migration:

The infused donor T cells interact with the primed APCs leading to the initiation of the second phase of acute GVHD. This phase includes antigen presentation by primed APCs, the subsequent activation, proliferation, differentiation and migration of alloreactive donor T cells. After allogeneic HSC transplants, both host- and donor-derived APCs are present in secondary lymphoid organs [15].

Phase 3: Effector phase:

The effector phase that leads to the GVHD target organ damage is a complex cascade of multiple cellular and inflammatory effectors that further modulate each other's responses either simultaneously or successively. Effector mechanisms of acute GVHD can be grouped into cellular effectors (e.g., CTLs) and inflammatory effectors such as cytokines [16].
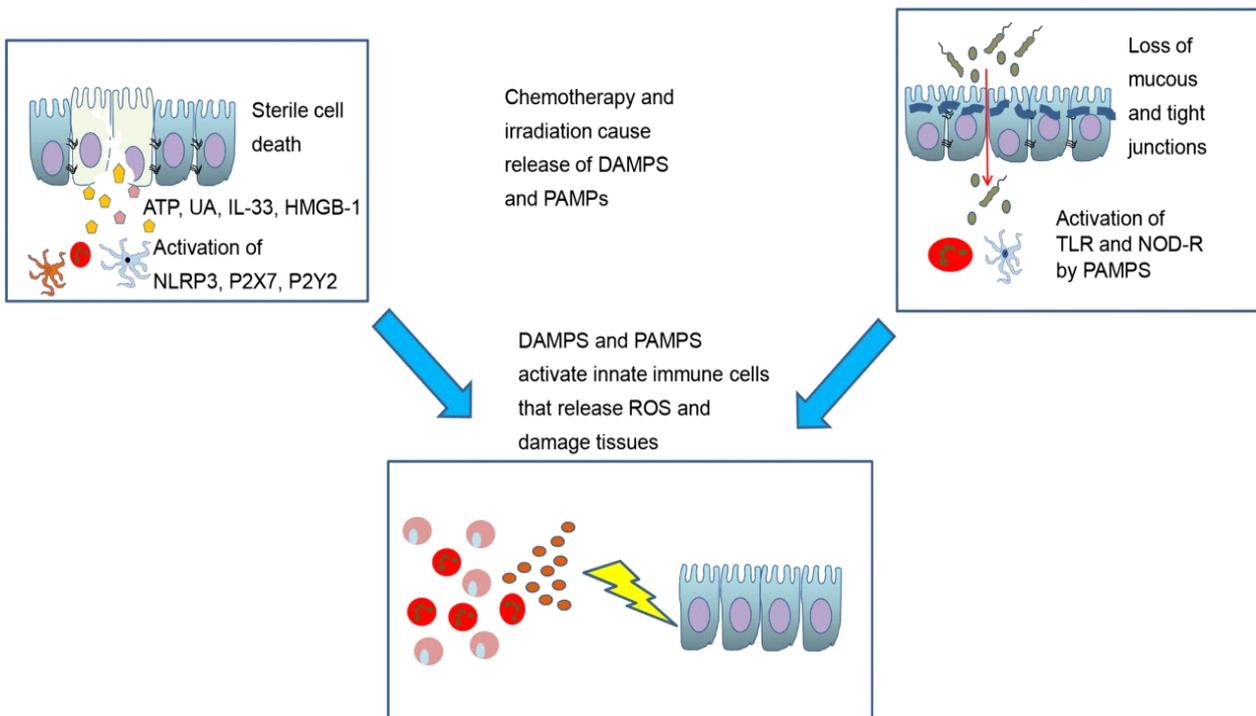

Figure (4): Schematic overview of the early steps in the pathogenesis host disease [16]

Mediators of inflammation:

Once activated, T cells initiate transcriptional programmes that result in the massive release of pro-inflammatory mediators [tumour necrosis factor α (TNF-α, TNF), interleukin 1 (IL1), γ interferon (IFN-γ, IFNG)] that amplify the immune response and result in tissue damage. In addition, cytokines and chemokines influence proliferation, differentiation and homing of effector cells to GVHD target tissues [17].

Epigenetic regulation of GVHD:

Epigenetic regulation of transcription is becoming increasingly implicated in the immunobiology of GVHD. Inhibition of proteins, which orchestrate methylation and acetylation of DNA and histones, exert widespread regulation over gene expression programmes that induce tolerance. Epigenetic states are malleable, thus it may be possible to use clinically available agents to reprogramme immune cells to limit GVHD [18].

Identification of biomarkers:

Although GvHD is the main complication of allogeneic SCT, non-relapse-related mortality (NRM) can occur independently from the occurrence of GvHD or in patients with minor GvHD. Overall, NRM has decreased in the last 10 years as a result of several improvements such as reduced intensity conditioning; resulting in reduced organ toxicity, improved donor selection and matching, and progress in supportive treatment. Major complications include viral and fungal infections, which can occur independently from GvHD due to the immunodeficiencies induced by HSCT. GvHD and its treatment aggravate and prolong the risk of infectious complications, and many patients suffering from severe GvHD die from infectious complications [1].

Role of microbiome in GVHD:

The interplay of the intestinal microbiome and GVHD has been a topic of investigation since the 1970s when **van Bekkum** [19] observed delayed GVHD after gut decontamination. Rigorous examination of the relationship between GVHD and microbiota has only been possible with recent advances in technology allowing for culture-independent rRNA gene sequencing. With this new tool, investigators have noted a profound loss of bacterial diversity in murine models of GVHD [20]. Specifically, higher proportions of bacteria belonging to the genus Blautia was linked to decreased GVHD-specific mortality and improved survival. Of particular clinical interest, loss of Blautia is associated with use of antibiotics targeting anaerobes as well as parenteral nutrition; suggesting two potential interventions to mitigate acute GVHD. However, murine experiments suggest that the donor microbiome does not seem to affect GVHD severity in the hosts [20]. In a murine model of GVHD, administration of this same cocktail was shown to reduce GVHD and improve survival [21].

Prophylaxis and treatment:

There are no standardized preventive measures for aGVHD. Prophylactic approach is based mainly on immunosuppression either by T cell depletion or pharmacologically. Immunosuppression remains the primary pharmacologic strategy to prevent GVHD. The most commonly includes a combination of a calcineurin inhibitor (cyclosporine (csa) or tacrolimus (TAc)) and a short course of methotrexate (MTX) [22]. The backbone of conventional regimens of aGVHD prophylaxis includes 2 drugs: a calcineurin inhibitor plus MTX or MMF or more recently sirolimus. The addition of steroids does not confer any beneficial effect [23]. Higher tacrolimus concentrations during the first week after allografting with a reduced-intensity conditioning regimen were associated with significantly reduced risk of grade II-IV aGVHD without increasing risk of relapse. This association was driven by a lower risk of grade II-iV aGvHD in patients with week 1 tacrolimus concentrations > 12 ng/ml [24].

The addition of sirolimus for GVHD prophylaxis in Ric AHscT is associated with a lower risk of acute GVHD, no improvement in survival and no increased overall toxicity. This regimen is an acceptable option for GVHD prevention in Ric HscT [25]. In aGVHD, treatment should always be tailored to the severity of the presentation and targeting the symptoms. Treatment consists of continuing the original immunosuppressive prophylaxis and methylprednisolone with the most common starting dose being 2 mg/kg/day given in 2 divided doses in grade III-IV, while 0.5 to 1 mg/kg/day for grade II disease [26].

Alternative therapies for steroid refractory cases include antithymocyte globulin (ATG), cyclosporine alone, mycophenolate mofetil, anti-iL-2 receptor, anti-cD5-specific immunotoxin, pan T-cell ricin A-chain immunotoxin, ABXcBL, etarnercept, infliximab, daclizumab, vilizumab and pentostatin. These agents can be used alone or in combination [27]. **Kitko and Levine** [28] reported success of extracorporeal photopheresis for steroid refractory aGVHD and the potential for delivery of Ecp in the early pre and post-transplant periods that shows promise as a less immunosuppressive strategy to reduce rates of aGVHD.

CONCLUSION

Acute graft versus host disease (aGVHD) remains the second leading cause of death following allogeneic hematopoietic stem cell transplant (AHSCT). Over the last five years, the progress in understanding the pathophysiology of this immune based-process helped redefine graft versus host reaction and opened new possibilities for novel preventive and therapeutic

approaches. The evolution in the field of immunology widened the horizons for hematopoietic stem cell transplant leading to the availability of different stem cell sources for potential graft and incorporation of novel conditioning regimens.

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