Published in final edited form as:

Best Pract Res Clin Haematol. 2013 September ; 26(3): . doi:10.1016/j.beha.2013.10.009.

Acute graft-versus-host disease: Are we close to bringing the bench to the bedside?

Anthony D. Sung, MD* [Fellow, Division of Hematologic Malignancies and Cellular Therapy] and **Nelson J. Chao, MD, MBA** [Donald D. and Elizabeth G. Cooke Professor, and Chief, Division of Hematologic Malignancies and Cellular Therapy/BMT]

Duke University Medical Center, Division of Hematologic Malignancies and Cellular Therapy, 2400 Pratt St, Suite 9100, Box 3961, Durham, NC 27710, USA

Abstract

Graft-versus-host disease (GVHD) is a major complication of allogeneic hematopoietic stem cell transplant (AHSCT) associated with significant morbidity and mortality. This review focuses on the pathophysiology, prevention, and treatment of acute GVHD. Specifically, we explain how new discoveries in immunology have expanded our understanding of GVHD, in which tissue damage from chemotherapy or radiation results in cytokine release, activating T cells, resulting in proliferation and differentiation, trafficking to target organs, and tissue destruction and inflammation. Insights into the mechanisms of this disease relate directly to the development of preventive strategies and therapies, such as immunosuppression, calcineurin inhibitors, T-cell depletion, CCR5 antagonists, gut decontamination, extracorporeal photopheresis, and more. Understanding the immunobiology of GVHD and developing effective preventions and treatments are critical to the continuing success of AHSCT.

Keywords

AHSCT; allogeneic hematopoietic stem cell transplant; calcineurin inhibitors; CCR5 antagonists; extracorporeal photopheresis; graft-versus-host disease; gut decontamination; GVHD; immunosuppression; pathophysiology; prevention; T-cell depletion; treatment

Introduction

Allogeneic hematopoietic stem cell transplant (AHSCT) has the potential to cure many hematologic malignancies. However, there is a risk of complications, particularly graft-versus-host disease (GVHD), in which donor-derived cells recognize recipient organs as foreign and mount an immune attack against the patient's own tissues. GVHD is a major cause of non-relapse morbidity and mortality, affecting 40%–60% of AHSCT patients [1] and accounting for 15% of deaths [2]. Acute GVHD, typically occurring between

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*Corresponding Author: Anthony D. Sung, Duke University Medical Center, Division of Hematologic Malignancies and Cellular Therapy, Durham, NC, USA, Tel: +1 919-684-8111, Fax: +1 919-684-3309, anthony.sung@duke.edu.

Disclosure:

Nelson J. Chao: Receipt of intellectual property rights: C2 Regenerate; Consulting fees: Cellerant Therapeutics; Contracted research: NIH.

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engraftment through 100 days after transplant, may have devastating consequences on the skin, gut, and liver. Chronic GVHD typically occurs after 100 days, though this temporal distinction is blurring with strategies such as reduced-intensity conditioning (RIC), and an overlap syndrome is recognized that shares features of both. This article focuses on the pathophysiology, prevention, and treatment of acute GVHD following AHSCT.

Pathophysiology

GVHD typically develops over five steps [3] (Figure 1). First, tissue damage from conditioning releases pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1), danger signals such as adenosine-5'-triphosphate (ATP) and nicotinic adenine dinucleotide (NAD), and extracellular matrix proteins such as biglycan that promote activation and maturation of antigen-presenting cells (APC) [4]. This is furthered by damage to the gastrointestinal epithelium, allowing translocation of lipopolysaccharide (LPS), activating toll-like receptors, furthering the cytokine cascade [5].

Second, donor T-cell activation is triggered by recipient antigens presented by host APCs [6] and sustained by donor APCs [7]. This is mediated by human leukocyte antigen (HLA) proteins encoded by the major histocompatibility complex (MHC); MHC compatibility is the most powerful determinant of GVHD, and there is a direct relationship between GVHD and mismatch at HLA-A, -B, -C, and -DRB1 (HLA-DQ and -DP appear to be less significant though still important) [8]. However, despite an 8/8 or even 12/12 match, 40% of recipients still develop GVHD [9], thought secondary to minor histocompatibility antigens (MiHA) [10].

T-cell activation also requires signaling between costimulatory molecules such as CD28 (T cell) and B7.1 or B7.2 (CD80 or CD86, APC); other T-cell:APC pairs include inducible costimulator (ICOS) (CD278):B7H (CD275), OX40 (CD134):OX40L (CD252), CD40L (CD154):CD40, and 4-1BB (CD137):glucocorticoid-induced tumor necrosis factor receptor (GITR) [11]. Absence of costimulatory signals, particularly CD28:B7.1/B7.2, can lead to anergy; furthermore, this interaction can be blocked by coinhibitory molecules such as CTLA4 (CD152), which competes with CD28 for B7.1/B7.2. Programmed death-1 (PD-1) (CD279): programmed death ligand 1 (PD-L1) (B7H1, CD274) are another pair of inhibitory molecules that can induce anergy or tolerance. Models that block these costimulatory or coinhibitory interactions have been shown to reduce or exacerbate GVHD, suggesting possible therapeutic targets [11].

Third, T cells proliferate and differentiate into naïve, effector, memory, regulatory, Th1/Tc1, Th2/Tc2, Th17, and other subsets. Naïve CD44^{lo}CD62L^{hi}CD8⁺ T cells appear to be essential to this response [12]; interestingly, CD44^{hi}CD62L^{lo} effector memory and CD44^{hi}CD62L^{hi} central memory T cells may promote graft-versus-tumor (GVT) without GVHD [13]. The balance between Th1/Tc1 and Th2/Tc2 subsets as well as Th17 subsets and the productions of cytokines such as IL-4, IL-5, IL-6, IL-12, IL-13, IL-17, IL-21, IL-23, TNF- α , transforming growth factor- β (TGF- β), and interferon- γ (IFN- γ) have been shown to impact GVHD, although the various contributions of each of these elements is still under investigation [14].

Fourth, activated T cells migrate from secondary lymphoid organs to target tissues (skin, liver, gut) through a combination of chemokine-receptor, selectin-ligand, and integrin-ligand interactions [15]. Selectins and integrins mediate rolling and tethering of lymphocytes along high endothelial venules (HEV) through interactions with their matching ligands. For example, interactions between L-selectin (CD62L) and α 4 β 7 integrin expressed on T cells and peripheral node addressin (PNAd) and mucosal addressin cell adhesion molecule (MAdCAM) expressed on secondary lymphoid tissue mediate homing to mesenteric lymph

nodes and Peyer patches and induction of gut GVHD [16]. Lymphocyte chemotaxis receptors such as CCR5, CCR6, and CCR7 are also essential to T-cell trafficking between secondary lymphoid tissues and target organs [17–19].

Fifth, once they reach target organs, T cells cause tissue destruction through direct cytotoxic activity as well as recruitment of other leukocytes. Cytotoxic activity is largely mediated by the Fas ligand (FasL):Fas and perforin-granzyme pathways [20]. Interestingly, other cytolytic pathways such as TNF-related apoptosis-inducing ligand (TRAIL) may preferentially mediate GVT but not GVHD [21]. Cytokines such as TNF- α , IFN- γ , IL-2, IL-7, IL-10, and others also appear to be essential to regulating leukocyte recruitment and tissue destruction; these effects are dependent on strength, timing, and other interactions, making the effects of individual cytokines difficult to predict [3].

Parallel to T-cell activation is the induction of tolerance and anergy [22]. These negative feedback mechanisms are crucial to prevent excessive tissue destruction and autoimmunity. Central deletion of auto-reactive T cells occurs in the thymus, and loss of thymic repertoire selection has been shown to contribute to GVHD [23]. Peripherally, FoxP3⁺ regulatory T cells (Tregs) have been found to suppress GVHD [24]. Co-inhibitory signals as noted above also play an important role.

B cells are also involved in antigen presentation, cytokine secretion, and antibody production [25–27]. A retrospective analysis suggested that the concentration of infused B cells may predict the incidence of GVHD [28], and correlations have been reported between high levels of B-cell activating factor (BAFF) and chronic GVHD [29]. Furthermore, rituximab conditioning as part of AHST for follicular lymphoma has been associated with an intriguingly low rate of GVHD (11%) [30], though further studies are needed, and data from murine studies on the role of recipient B cells in GVHD are mixed [31,32].

Predictive Factors

HLA mismatch is the strongest determinant of GVHD. Minor antigen mismatch also increases the risk of GVHD, as seen with sex-mismatched and unrelated donors [33]. Donor multiparity has been linked with increased risk of GVHD secondary to maternal alloimmunization [34]. However, in haploidentical transplantation, mismatches in noninherited paternal antigens increase the risk of GVHD compared to noninherited maternal antigens (NIMA), suggesting that in-utero exposure to NIMA may exert more complicated effects [35]. Use of umbilical cord blood appears less likely to cause GVHD, and 4/6 mismatches can be tolerated with this donor source [36].

In addition to donor characteristics, other factors have been associated with the risk of GVHD. Reduced intensity conditioning causes less damage and less GVHD [37], while total body irradiation causes more GVHD [33]. Polymorphisms in cytokine genes have been shown to affect the severity of GVHD [38].

Full donor chimerism is associated with a higher incidence of GVHD than mixed chimerism (in which mixed populations of donor and recipient cells are detected) [39]; however, mixed chimerism is associated with higher rates of engraftment failure and relapse. Attempts to convert mixed to full donor chimerism or to treat relapse with donor lymphocyte infusion often increase GVHD [40,41]. The intestinal microflora also affects GVHD [42]; this can be attenuated by antibiotics [43]. Additionally, CMV positivity in either the donor or recipient increases the risk [44]. Older patients are more likely to have GVHD [33], possibly due to increased thymic involution with aging and impaired central deletion of auto-reactive T cells. Patients with worse performance status are also at higher risk [44].

Plasma biomarkers, although not widely adopted, are a promising area of research: elafin (also known as peptidase inhibitor-3, skin-derived antileukoproteinase, or trappin-2) is elevated 3-fold in skin GVHD [45] and regenerating islet-derived 3- α (REG-3 α) is increased 3-fold in patients with gastrointestinal (GI) GVHD [46]. The combination of these two proteins with IL-2 receptor- α , TNF receptor-1, hepatocyte growth factor, and IL-8 form a 6-protein biomarker panel that predicted response to GVHD treatment and mortality in a randomized clinical trial [47].

Prevention of GVHD

Prevention focuses on targeting T cells. Methotrexate has been used since the 1950s [48] and in combination with cyclosporine or tacrolimus since the 1970s, forming the cornerstone of most prophylactic regimens [49]. However, these agents have numerous side effects, including delayed cell count and immunological recovery, thrombotic microangiopathy [50], and posterior reversible encephalopathy syndrome [51]. Mycophenolate mofetil and sirolimus have been proposed as alternate agents [52,53]; however, there is no clear consensus on optimal drug combination, dosing, or timing. Post-transplant cyclophosphamide is another method of targeting T cells that showed promise in recent clinical trials [54].

Another option is to remove T cells from the graft, known as T-cell depletion (TCD). In randomized trials, TCD decreases the risk of GVHD, although it increases the risks of graft failure, disease relapse, and opportunistic infections [55,56]. Nonetheless, TCD can facilitate transplants from HLA-mismatched haploidentical donors without significant GVHD [57], opening up transplant options to patients without HLA-matched donors.

Other strategies target cytokine/chemokine-receptor interactions. Reduced intensity conditioning causes less tissue damage, less cytokine production, and less GVHD [58]. Similarly, gut decontamination with ciprofloxacin and metronidazole decreases the risk of acute GVHD compared to ciprofloxacin alone [43]. Exciting results have been reported with maraviroc, a CCR5 antagonist that blocks T-cell chemotaxis and dramatically decreased the incidence of gastrointestinal and liver GVHD [59]. At the same time, drugs that block central cytokine pathways, such as etanercept and infliximab, failed to improve rates of acute GVHD [60,61]. Intravenous immunoglobulin (IVIG) reduces GVHD but raises questions of cost and humoral immunity [62].

New strategies are under exploration. Soluble CTLA4 targeting the CD28:B7 costimulatory pathway successfully induced anergy and resulted in a low rate of GVHD in a single-arm trial [63]. Multipotent mesenchymal stromal cells (MSC) can differentiate into a variety of supportive cells and exert immunosuppressive effects on both lymphocytes and APCs. In a randomized phase II trial, prophylactic MSC resulted in 5.3% grade II–IV GVHD compared to 38.9% in controls [64].

Treatment of GVHD

Glucocorticoids are the backbone of treatment of GVHD [65]. Unfortunately, only about half of patients respond [66], and there is no clear second-line agent for steroid-refractory GVHD. Many single-arm trials have shown benefit with immunomodulators, such as anti-thymocyte globulin, tacrolimus, sirolimus, or mycophenolate mofetil, or antibody therapy against CD3, CD7, CD52, CD147, IL2-R, IL1, and TNF α , though none have proven efficacy in randomized trials [67].

Novel approaches are currently under investigation. Adoptive transfer of Tregs has shown safety and decreased rates of GVHD compared to historical controls [68]. Extracorporeal

photopheresis exerts a number of immunomodulatory effects, including lymphocyte apoptosis, increasing Tregs, and shifting from a Th1 to Th2 phenotype [69]; studies are now looking at this strategy for prevention [70]. Denileukin diftitox, a recombinant protein composed of IL-2 fused to diphtheria toxin, is another novel approach that showed promise in a phase II trial [71], as is pentostatin, a purine analog [72]. Phototherapy using ultraviolet A (UVA) irradiation with or without psoralen (PUVA) appears to help cutaneous lesions [73], and oral beclomethasone may improve gastrointestinal GVHD [74]. Finally, in addition to use as prophylaxis, mesenchymal stem cells have been used for treatment of GVHD.[75,76].

Preclinical studies suggest IL-21 blockade may increase FoxP3+ inducible Tregs in vivo and decrease GVHD [77,78]. Histone deacetylase inhibitors can also enhance Treg function and induce tolerance [79]. ICOS blockade can inhibit expansion of effector T cells in secondary lymphoid organs, thereby reducing GVHD [80]. Other strategies target innate immunity by blocking antigen presenting cell derived complement [81]. Administration of CSF-1 can expand host macrophages and decrease GVHD [82].

Supportive care is critical. This includes gut rest, hyperalimentation, and fluid and electrolyte repletion for gastrointestinal GVHD; octreotide may also help [83]. Prophylaxis against infections and early intervention when infections are suspected are essential, and treatment of hypogammaglobulinemia with IVIG may be helpful. Providers should closely monitor patients for side effects of immunosuppressants.

Future Directions

As our ability to prevent and treat GVHD improves, it is important to keep in mind the ultimate goal: curing our patients. As experience with TCD has shown, methods that lower GVHD may also lower GVT, thereby increasing the risk of relapse of hematologic malignancies. Further insights are needed to not just treat GVHD, but to treat GVHD while maintaining or maximizing GVT; this separation remains the holy grail of AHSCT.

Acknowledgments

The authors would like to thank Joel Ross, Ph.D., for his artistic assistance with the figure. Dr. Sung's effort was supported by NIH T32 HL007057-37.

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Fig. 1. Pathophysiology of acute GVHD

Chemotherapy and radiation cause tissue damage, producing pro-inflammatory cytokines, resulting in **T-cell activation** through APC-T cell interaction via MHC-T cell receptor binding and co-stimulatory signals. This leads to **T-cell expansion and differentiation** into various subtypes, which **traffic** through blood vessels to target organs, where they cause **tissue destruction and recruitment** of other inflammatory cells through pathways such as perforin/granzyme and cytokine release. These inflammatory cells and cytokines can further propagate the cycle of GVHD. This process is internally regulated by **T_{reg}** cells as well as **thymic deletion** of alloreactive T cells. Exogenous means of treating GVHD include inhibitors of inflammation and cytokines, immune checkpoint modulators, calcineurin inhibitors, and CCR5 inhibitors.

Abbreviations: APC, antigen presenting cell; CCR5, chemokine receptor type 5; IFN γ , interferon γ ; MHC, major histocompatibility complex; T_{CM}, central memory T cell; T_{EM}, effector memory T cell; T_{reg}, regulatory T cell; TNF α , tumor necrosis factor α ; TRAIL, TNF-related apoptosis inducing ligand.