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Overview of Progress in Chronic Graft-Versus-Host Disease

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Abstract

cGVHD is now known to be a more complex immune reaction. Thymic damage and aberrant antigen presentation leads to aberrant T- and B-cell reaction characterized by Th17/Tc17 differentiation, macrophage sequestration in tissue, alloantibody formation and TGF β -dependent fibrosis. Inadequate peripheral tolerance resulting from Treg dysfunction or reduced numbers and reduced ratios of Tregs to T effector cells also play a role.

Abbreviations: GVHD: Graft-Versus-Host Disease; cGVHD: Chronic GVHD; GVL: Graft-Versus-Leukemia; alloSCT: Allogeneic Hematopoietic Stem Cell Transplantation; APC: Antigen-Presenting Cell; NIH: National Institutes of Health; CXCL9: C-X-C Motif Ligand 9; BAFF: B-cell Activating Factor; CTLA-4: Cytotoxic T-lymphocyte associated Protein-4; DCs: Dendritic Cells; CSF-1: Colony-Stimulating Factor 1; NK: Natural Killer; Bregs: Regulatory B Cells; TFR: T Follicular Regulatory; TFH: T Follicular Helper; Fc: Fragment Crystallizable of Immunoglobulins; GC: Germinal Center

Introduction

AlloSCT is the curative option for various benign and malignant hematologic disorders [1] with its curative potential depends on the GVL effect [2]. Unfortunately, GVHD remains a major cause of morbidity and mortality following HSCT [3]. cGVHD occurs in 20–50% of recipients depending on the type of transplant, patient characteristics, and GVHD prophylaxis regimen [3]. The incidence of cGVHD is increasing because of the older age of patients being transplanted, the use of mismatched and unrelated donors (as opposed to matched siblings) and the predominant use of PBSCs. Allogeneic PBSC transplantation is relatively enriched for the TH2 population, which may account for the relatively moderate rate of acute GVHD seen after the large T-cell load given with the peripheral blood [4]. The greatest risk factor for development of cGVHD is prior acute GVHD [4]. Other risk factors for cGVHD development include transplant of female donors to male recipients, and absence of antithymocyte globulin in conditioning [5].

Pathogenesis

cGVHD reflects the inability to achieve immune tolerance after alloSCT resulting in the persistence of allo and auto-reactive T and B cells [6]. In cGVHD, there is a preponderance of evidence for interplay between donor T cells and donor B cells for disease pathogenesis [5]. The pathogenesis of cGVHD shares similarities with acute GVHD [7]. cGVHD and acute GVHD may share initiating mechanisms. For e.g., Th17/Tc17 cells have been shown, in some systems, to cause either acute GVHD or sclerodermatous cGVHD [5]. The immunologic mechanisms that result in cGVHD share many features with common autoimmune diseases, where defects in immune tolerance combine with adaptive immune responses targeting auto antigens to produce chronic tissue damage [8]. Donor NK cells, Tregs, Bregs, and macrophages play important roles in dampening both acute GVHD and cGVHD [5].

cGVHD is an inflammatory disorder initiated by APC activation of alloreactive T cells [7]. Donor alloreactive T cells are the key drivers in the development of cGVHD since they recognize and damage the host target tissues by cytokine release and direct cytolysis [9]. Mature donor T cells within the graft contribute to thymic destruction resulting in disrupted immune reconstitution. Thymic dysfunction favors the selection of auto reactive and alloreactive T cells polarized toward Th17/Tc17 lineages. Polyfunctional Th17/Tc17 cells migrate to target organs where secreted IL-17 may function as a monocytes chemokine to promote monocyte adhesion [5].

Both host and donor APCs specifically DCs, the most potent APCs, are important regulators of GVHD (10). Donor-derived DC APC [10] function is corrupted during acute GVHD, reducing

their capacity to expand and maintain Tregs in the periphery [5]. Reduction or loss of this population of T cells is associated with loss of immune tolerance and development of autoimmunity [3]. Altered Bregs and NK development after SCT is thought to contribute to cGVHD [5]. Patients with cGVHD had reduced levels of circulating IL-10–producing Bregs and impaired IL-10 production [3].

TFR regulate the GC reaction and suppress B cell differentiation and immunoglobulin secretion. This suppressive subset is deficient in cGVHD due to altered TFR survival, thus favoring imbalance toward TFH effectors [6]. TFH cells migrate to GC, where they promote GC reaction in vivo resulting in differentiation of mature B cells and secretion of high-affinity immunoglobulin G antibodies [8]. The levels of circulating TFH cells are decreased in active cGVHD, but these TFH cells are activated and have increased functional ability to promote B-cell maturation [8] and stimulate B cells to produce auto and allo-antibodies involved in cGVHD [6].

Patients with active cGVHD had significantly elevated levels of BAFF and increased signaling through the ERK and AKT pathways (both are activated via BAFF) which was associated with decreased apoptosis of activated B cells [3]. TFH-derived IL-21 together with elevated levels of BAFF, result in aberrant B-cell reconstitution favoring GC B-cell expansion [5]. Plasma cell–derived allo/autoantibodies in concert with CSF-1-dependent donor macrophages induce TGF β , high environment locally within target tissue that results in scleroderma and bronchiolitis obliterans, diagnostic features of cGVHD [5].

Clinical Features

Acute GVHD and cGVHD are no longer defined by their time of onset but rather by their clinical features [4]. cGVHD typically manifests with multiorgan pathology. The commonly seen diagnostic features, as outlined by the NIH consensus criteria, include skin pathology varying from lichen planus–like lesions to full sclerosis, bronchiolitis obliterans, and oral lichen planus–like lesions (i.e., skin, lung, and mouth involvement). Esophageal webs and strictures and muscle or joint fasciitis are also diagnostic [5]. The NIH panel recommends at least one diagnostic manifestation of cGVHD or at least one distinctive manifestation proved with a pertinent biopsy, laboratory, or other tests (e.g., pulmonary function tests, Schirmer's test) evaluated by a specialist or radiographic imaging showing cGVHD [11].

The NIH Global Severity Index of cGVHD categorizes the disease as mild, moderate, or severe. Mild cGVHD includes the involvement of one or two organs, moderate cGVHD involves three or more organs or at least one organ with a score of 2, and severe cGVHD includes one organ score of 3 or a lung score of 2 or 3. According to this index, 2-year overall survival was 62%, 86%, and 97% for patients with severe, moderate, and mild disease, respectively [11]. These diagnostic features can be seen before day 100 and may occur simultaneously with features commonly seen in acute GVHD (e.g., macular-papular rashes, weight loss, diarrhea, and hepatitis). Thus, cGVHD occurs as a continuum in time with clinical features that are distinct from, but not mutually exclusive with, those seen in acute GVHD [5]. Two subcategories of cGVHD (classic and overlap acute or chronic) are recognized [4]. Patients with overlap syndrome have worse survival and higher non-relapse mortality [11].

Biomarkers

Some centers use one or more of pretransplant clinical risk factors for GVHD including the degree of HLA match between donor and recipient, recipient age, donor type, and conditioning regimen intensity as predictors of non-relapse mortality [2]. They are incomplete guides for predicting outcomes. Biomarkers may refine the ability to determine the likely outcome of the individual patient, making possible the prevention of complications by individualizing the treatment approach [12].

Several biomarkers, such as soluble B-cell activation factor, antidouble-stranded DNA antibodies, soluble IL-2 receptor alpha, soluble CD13, adiponectin, and soluble CXCL9, have been explored to describe cGVHD; however, none of them are in clinical use [11]. The role of chemokine CXCL9 as a gatekeeper for tissue distribution of alloreactive T cells in cGVHD is supported by the high levels of CXCL9 seen in oral, ocular, and mucosal cGVHD [12]. Increased true naïve cells (TN), stem cell memory cells (SCM), effector memory cells (EMRA) CD8 subsets very early after HSCT in patients who subsequently develop cGVHD suggest the possibility that these may be relevant biomarker for cGVHD development [13].

Treatment

Despite advances in the understanding of the pathobiology of cGVHD, there have been relatively few advances in its clinical management [8]. Progress in improving cGVHD prevention and therapy has been hindered by complexities in cGVHD diagnosis and staging, lack of uniform treatment response criteria, paucity of controlled trials, and access to new therapies with an established proof-of-concept or strong pathophysiological basis in preclinical models [5].

Corticosteroids and meticulous organ-specific care remains the mainstay of therapy. Corticosteroids are profoundly anti-inflammatory, immune suppressive, affecting both innate and adaptive immunity. The addition of a calcineurin inhibitor to corticosteroids does not increase the response rate, but reduces steroid dosing and the sequelae of chronic corticosteroid therapy. Therapy of corticosteroid-resistant cGVHD has relied primarily on broadly immune suppressive agents and specific inhibitors of T-cell signaling (such as tacrolimus and calcineurin inhibitors). There are no standard second line therapies for advanced cGVHD. The efficacy of second-line agents is limited, with response rates of ~30% regardless of the agent that is chosen [8].

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The major cause of death in patients with cGVHD is infection from the profound immunodeficiency associated with cGVHD and its therapy. Careful monitoring with antibiotic prophylaxis for encapsulated organisms is warranted in all patients. Patients should remain on prophylaxis for viruses, P. jirovecii pneumonia, and fungal infections (yeast and mold). Patients with frequent infections and low immunoglobulin levels may benefit from intravenous immunoglobulin replacement [4].

Future approaches to reduce the incidencecGVHD

- Direct removal of naive α β T cells from the graft (e.g., using in vitro magnetic-based antibody or CD34+ stem cell selection) can prevent cGVHD (5).

- Depletion of differentiating T-cell in vivo with antithymocyte globulin administered in the peritransplant period to promote engraftment and prevent acute GVHD (8).

- Selective depletion of alloreactive T cells in the early posttransplant period by administration of posttransplant cyclophosphamide (8) to preferentially deplete alloreactive T cells while sparing Tregs(5) and in vitro treatment of alloantigen-activated donor T cells with a photosensitizer (TH9402) (8).

- Inhibit the more terminal stages of aberrant (Th17/TFH) T-cell development include small-molecule ROR γ τ or STAT3 inhibitors and antibody-based therapeutics targeting IL-17 or IL-21 and their receptors (5).

- JAK inhibition is associated with reductions in the severity of cGVHD and prolonged survival, without interfering with beneficial GVL activity. JAKs are important for the intracellular transduction of many cytokines that regulate the development and function of immune cells involved in GVHD, including DCs, macrophages, T cells, B cells, and neutrophils. However, further data from prospective trials is important to confirm effectiveness (7).

- Decreased Treg may be rescued by low-dose IL-2 administration resulting in improved Treg number and survival (6). ~50% of patients showing Treg expansion and some clinical response as long as therapy is continued. Adoptive transfer of Tregs with or without IL-2 and/or rapamycin has begun to be tested in clinical trials in an effort to increase the proportion and depth of patient response (5). Treg adoptive therapy enhances Treg numbers after SCT and reconstitutes the Treg pool. Treg adoptive transfer can prevent and treat cGVHD in mice with multiorgan system disease (5).

- Immune checkpoint blockade: CTLA-4 is a negative regulator of T-cell immune function. CTLA-4 is homologous to CD28, but binds with a greater affinity and avidity than CD28. It is expressed on activated T cells and binds to CD80/CD86 on APCs, thereby blocking the interaction with CD28, and inhibits T-cell proliferation, differentiation and survival. Abatacept is a selective costimulation modulator composed of human CTLA-4 and a fragment of the fragment crystallizable (Fc) domain of human immunoglobulin- G1. It could be a potential therapeutic option (3).

- Strategies to inhibit or prevent migration of TFH cells to lymphoid organs have been effective in preclinical models and may prove useful for cGVHD prevention or therapy in the future (8).

- Prevention of aberrant B-cell development by administration of CD20 monoclonal antibody. It reduces cGVHD severity when used as a preventative but not treatment strategy; this is likely due to the more effective B-cell depletion rather than antibody-secreting plasmablasts and plasma cells formed after cGVHD is established (5).

- Pharmacological agents that inhibit B- (with or without T-) cell activation, differentiation, and GC integrity by kinase inhibition (eg, Syk kinase, fostamatinib; and Bruton kinase; ibrutinib). Promising early clinical results already achieved with ibrutinib(5).

- At the most final stage of aberrant B-cell response, depletion of alloantibody producing plasma cells by proteosome inhibition (eg, bortezomib) is supported by evidence of efficacy in animal systems and early clinical studies (5). Proteasome inhibitors have been shown to have immune-modulating effects inmurine models of cGVHD, including deletion of alloreactive T cells, inhibition of APCs, inhibition of IL-6, increased survival of Tregs, and decrease in levels of BAFF (3).

- Targeting macrophages by preventing differentiation and survival in tissue through the inhibition of CSF-1R has proven highly effective in animal systems, as has the inhibition of TGF β (5).

- There are underway trials evaluating mesenchymal stem cells for treatment of cGVHD (3). Several groups have reported its efficacy for cGVHD (14).

Conclusion

Further evaluation of these new therapeutic modalities in prospective multicenter trials are needed to identify their effectiveness in improving outcomes of patients with cGVHD.

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