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New in Acute Graft-Versus-Host Disease

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Abstract

Life-threatening complications, such as GVHD, infection, conditioning regimen-related toxicities, and transplant-associated thrombotic microangiopathy are limiting factors for the clinical application of the HCT. They are more common in patients receiving HLA locus mismatched grafts.

Abbreviations: GVHD: Graft-Versus-Host Disease; aGVHD: acute GVHD; HCT: Hematopoietic Cellular Transplantation; HR: High Risk; NRM: Non Relapse Mortality; SR: Steroid Refractory; GVL: Graft-Versus-Leukemia; allo-SCT: Allogeneic Hematopoietic Stem Cell Transplantation; APC: Antigen-Presenting Cell; GI: Gastrointestinal; REG3α: Regenerating Islet-Derived 3-Alpha; ST2: Suppression of Tumorigenicity 2; IL: Interleukin; pTCy: Post Transplantation Cyclophosphamide; MAGIC: Mount Sinai Acute GVHD International Consortium Algorithm; mAb: Monoclonal Antibody; HLA: Histocompatibility Leukocyte Antigens; AAT: Alpha-1 Antitrypsin; ORR: Overall Response Rate; BAFF: B-Cell Activating Factor; MSCs: Mesenchymal Stromal Cells; FMT: Fecal Microbiome Transplantation.

Introduction

HCT is an effective and curative treatment of different malignant and non-malignant diseases [1]. Its curative potential depends on the GVL effect [2]. GVHD, traditionally known as an immune cells-mediated immune injury, is a major complication after allo-SCT [3]. Despite prophylactic treatment, aGVHD affects 30-70% of recipients [4].

Pathogenesis

Following SCT, tissue injury and inflammation initiated by the conditioning regimen results in release of proinflammatory cytokine (e.g., tumor necrosis factor, IL-6, and IL-1). These cytokines, together with luminal damage-associated molecular patterns and pathogen-associated molecular patterns released from damaged gut tissue and the microbial luminal contents, result in the activation of APCs [5]. These cytokines also provoke increased MHC expression and up regulate other adhesion molecules that, in turn, amplify recognition of allogeneic minor HLA differences by T-cells in the donor graft [4]. The reactive donor T-cells preferentially drive T-helper 1 (Th1)/T-cytotoxic 1 (Tc1) and Th17/Tc17 [5] to proliferate and secrete more cytokines that further activate additional donor T-cells and other inflammatory cells, including macrophages. This cascade [4] can eventually mediate target tissue GVHD, including the thymus and secondary lymphoid organs, as well as the skin, liver, gastrointestinal tract, and lung [5]. Many investigators consider aGVHD as a "cytokine storm" [4] aGVHD is generally defined as a Th1/Th17 paradigm, which results in extensive tissue destruction characterized by apoptosis [5].

Clinical Features

The median onset of aGVHD is approximately 1 month after transplant. aGVHD is no longer defined by its time of onset but rather by its clinical features. It is now recognized that typical features of aGVHD can occur after day 100. Two subcategories of acute (classic and persistent or late onset or recurrent) are recognized. Classic aGVHD occurs before day 100, and late aGVHD is defined as symptoms of aGVHD after day 100 [4]. aGVHD is characterized in its mildest forms by skin rash. As the disease worsens, the confluent rash may progress to blistering of the skin similar to a severe burn, profound diarrhea with crampy abdominal pain, and hepatic dysfunction with marked hyperbilirubinemia. aGVHD is graded by the extent of skin rash, the amount of diarrhea, and the degree of bilirubin elevation [4].

The Risk Score of aGVHD

Standard risk was defined as single-organ involvement (stage 1–3 skin or stage 1–2 GI) or two-organ involvement (stage 1–3 skin plus stage 1 GI or stage 1–3 skin plus stage 1–4 liver); all others were defined as high risk. Standard-risk patients had a day 28 ORR of 69% versus 43% in high-risk patients [6].

aGVHD Biomarkers

Pretransplant clinical risk factors for GVHD used to guide GVHD prophylaxis by some centers [2] are incomplete guide for predicting outcomes. Biomarkers may improve the ability to determine the likely outcome of the individual patient, making the prevention of complications possible [7]. By utilizing new therapies based on risk stratification models, outcomes may be improved, while toxicity is minimized [6].

The GI tract is a key to overall GVHD severity because it is affected in 86% of severe cases. One attractive strategy is to interrupt traffic of GVHD effector cells to the GI tract [2] Both ST2 and REG3α are closely associated with GI GVHD [2]. ST2 in plasma is the soluble form of IL-33 receptor. It acts as a decoy receptor for IL-33 by preventing the binding of IL-33 to T cells [7].

ST2 is shed from activated T cells as GVHD progresses [2]. ST2 is validated as a predictor for aGVHD, in particular, SR GVHD and NRM [7]. REG3α is produced by GI epithelium, in particular Paneth cells, whose numbers decrease significantly during GVHD. REG3α production decreases during GVHD even as its concentration increases in the bloodstream as a result of damaged epithelial mucosa [2]. Reg3α is validated as a predictor of GI GVHD [7]. IL-22 is a cytokine produced by cells of the adaptive and the innate system including CD4+ T cells, CD8+ T cells, natural killer cells, and gamma-delta (γδ) T cells. It serves an essential role in host defense against extracellular pathogens, strengthens epithelial barrier function by acting upon intestinal stem cells, and helps tissue repair and wound healing [6]. IL-22 induces REG3α and lowers numbers of circulating, IL-22–secreting innate lymphoid cells after transplant which is associated with a higher risk for GVHD [2].

The MAGIC Algorithm

2-biomarker model using ST2 and REG3α concentrations at day 7 after HCT could facilitate preemptive intervention for GVHD prior to the onset of clinical disease in a substantial number of patients. The levels of ST2 and REG3α biomarkers' concentrations both on day 7 and at the onset of overall symptoms were speculated to reflect GI pathology that is not yet clinically apparent [2]. Increase sensitivity of the algorithm in the future might include the incorporation of additional biomarkers or repeating the test at a later time point [2].

The Ann Arbor biomarker risk score based on plasma levels of tumor necrosis factor receptor-1, REG3α and ST2 has been validated. A risk score of 3 was associated with a less durable response (a complete response for ⩾6 months without recurrence of symptoms), higher likelihood of later developing SR lower GI GVHD and an NRM of 46% at 6 months regardless of clinical severity of GVHD [6]. Low AAT plasma levels in human donors were found to be associated with a higher rate of aGVHD in recipients. GVHD severity increased with decreasing AAT levels as well [6]. Patients with aGVHD had a higher percentage of CD30 expressing CD8+ T cells, significantly higher plasma levels of soluble CD30, and increased CD30+ lymphocytes in affected intestinal tissue compared with patients without aGVHD [6].

Treatment

Corticosteroids are the first-line therapy for aGVHD despite suboptimal response rates of 40–60%. The likelihood of response to treatment decreases with increasing severity of aGVHD [6]. Steroid-refractory aGVHD was defined as patients with aGVHD not responding to high-dose steroid treatment (≥2mg/kg per day) for 5 to 7 days, or with progression of at least 1 grade within 72 hours after the start of high-dose steroid treatment. The outcome for corticosteroids non responder patients is poor, with a reported 2-year survival of less than 20% [8]. Response rates with second-line treatments are low [6]. No second-line therapy has been proven superior to another for the treatment of SR-aGVHD, and choice of therapy is often based on patient specific characteristics, side-effect profile, and physician preference [6]. Intensification of immunosuppressive therapy in these patients for example by increasing the doses of steroids, or adding antithymocyte globulin, infliximab, or daclizumab to steroids did not improve response rates, but did increase the risk for infectious complications [8].

Novel aGVHD Prophylaxis Regimens

Novel prophylaxis regimens can preferentially facilitate Treg recovery after HSCT [9]. Prophylaxis against aGVHD, including protection against subclinical immune organ damage, may greatly reduce the incidence and/or severity of cGVHD [10]. pTCy selectively depletes activated alloreactive T cells while sparing resting T cells and hematopoietic stem cells. Its GVHD protective effect appears to be Treg dependent due to the differential expression of aldehyde dehydrogenase in Tregs compared with conventional CD4 T cells. This difference protects Tregs and facilitates their subsequent expansion. pTCy is frequently used in haploidentical bone marrow transplantation and is prospectively evaluated in patients with HLA-matched donors [9].

Fecal Microbiome Transplantation (FMT)

Therapy with metronidazole failed in most patients with C. difficile infections. Use of metronidazole was correlated with an increased incidence of aGVHD. Based on European Society of Clinical Microbiology and Infectious Diseases guidelines, patients with C. difficile infections after HCT should be treated as a high-risk group for severe complications. More potent oral vancomycin or novel therapies (e.g., fidaxomicin) should be administered instead of metronidazole as the first line therapy [11]. Increased abundance of intestinal Blautia (a member of the Clostridia class) is associated with reduced GVHD mortality and

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improved OS [11]. FMT has been investigated as a method to restore the composition of the gut microflora , and may eradicate multidrug-resistant bacteria before HCT, leading to reduction in aGVHD and TRM. Successful use of FMT for steroid-resistant gut aGVHD, C. difficile infection, or for decolonization of resistant pathogens has been reported [11].

Steroid-Free Acute Graft versus Host Disease Therapy

The biomarkers for HR disease may identify additional pathways that could be therapeutically targeted [6].

Cytokine Modulation

Soluble ST2 administration has been shown to reduce experimental GVHD. Additional strategies may target IL-33, which is released from dying GI epithelial cells during GVHD [2]. Administration of IL-22 restores REG3α homeostasis and accelerates repair of the epithelial mucosa, preventing GVHD in preclinical models [2]. There is also a potential relationship between IL-22 and the microbiome, as microbacteria has been shown to induce IL-22 secretion that then induces the production of antimicrobial proteins [6]. A phase I/II clinical trial (ClinicalTrials.gov identifier: NCT02406651) evaluate the safety and feasibility of use of IL-22 in combination with corticosteroids for the treatment of newly diagnosed grade II–IV lower GI aGVHD [6].

Alpha-1 Antitrypsin (AAT)

Donors treated with AAT had an increase in Tregs, as well as a 50-fold increase of IL-10, favoring an anti-inflammatory profile [6]. Based on these observations, a prospective phase I/II dose-escalation study was performed to evaluate the use of AAT in the treatment of SR-aGVHD [6]. Sirolimus (rapamycin) is a mammalian target of rapamycin (mTOR) inhibitor that has immunosuppressive activity and antineoplastic properties. Inhibition of mTOR impairs T-cell signaling and its use as a prophylactic agent and as a second-line agent for SR-GVHD has been reported [6].

Kinase Inhibitors

JAK inhibition may be useful for treating patients with aGVHD; however, further data from prospective trials will be important to confirm its effectiveness [10]. JAK inhibition impairs the differentiation and function of dendritic cells, the most important APCs, causing reduced T-cell activation [6]. 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. JAK inhibition is associated with reduction in the severity of aGVHD and prolonged survival, without interfering with beneficial GVL activity (10) Preliminary studies support the efficacy of ruxolitinib for treatment of patients with grade 3/4 corticosteroid refractory-aGVHD. Adverse events were cytomegalovirus reactivation (33%), grade 3/4 cytopenia (33%), and grade 1/2 cytopenia (22%) [10].

Monoclonal Antibodies

Natalizumab is a humanized mAb against α4-integrin containing adhesion molecules widely expressed on leukocytes, primarily lymphocytes. Natalizumab might be able to mitigate GI GVHD by preventing homing of leukocytes to the GI tract [6]. Vedolizumab is a mAb that specifically inhibits α4β7 integrins located on activated T cells from interacting with MAdCAM-1 (located on gut epithelium) preventing homing to the intestinal mucosa [6]. Brentuximab vedotin is an anti-CD30 antibody–drug conjugate composed of the antimicrotubule agent monomethyl auristatin E (MMAE) and a human CD30 antibody [6].

Adoptive Cell Therapy

Mesenchymal Stromal Cells (MSCs)

MSCs are pluripotent stem cells capable of differentiation into multiple cell lineages of mesenchymal origin (osteoblast, chondrocytes, and adipocytes). They inhibit B and T-cell activation, block the function of APCs, inhibit natural killer cells, and increase Tregs. MSCs can be isolated and expanded ex vivo from bone marrow, umbilical cord blood, adipose tissue, and placenta. MSCs do not express class II HLA and therefore do not provoke immunologic responses in HLA-mismatched recipients [6]. MSCs have been shown to suppress T cell proliferation and natural killer cell function in vitro. Responsiveness of recipient lymphocytes to MSCs may be one factor to determine MSC treatment outcome, however, factors that determine such responsiveness are largely unknown. MSC treatment does improve the outcome in SR aGVHD patients [8]. MSC therapies have been studied in phase I and II trials for the treatment of SR-aGVHD with overall responses ranging from 60-75% [6]. Well-designed, prospective randomized clinical trials are needed to confirm the potential of MSCs as salvage therapy for SR GVHD and to identify those patients that will benefit most [8].

Proteasome inhibitors have been shown to have immune-modulating effects in murine models of aGVHD, including deletion of alloreactive T cells, inhibition of APCs, inhibition of IL-6, increased survival of Tregs, and decrease BAFF levels [6].

Conclusion

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

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