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Commentary

Advances in Understanding and Managing Graft-*versus*-Host Disease after Allogeneic Stem Cell Transplantation

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DESCRIPTION

Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) remains the only curative option for many patients with leukemia and other hematologic malignancies. However, its therapeutic potential is significantly limited by Graft-*Versus*-Host Disease (GVHD), a systemic inflammatory condition resulting from donor T-cell recognition of recipient antigens. Despite decades of research and clinical advances, GVHD continues to affect 30-70% of allogeneic HSCT recipients and remains a leading cause of non-relapse mortality. Recent advances in understanding the pathophysiology of GVHD have led to novel preventive and therapeutic approaches that are transforming the management of this challenging complication.

The classical model of acute GVHD pathophysiology describes a three-phase process: tissue damage from conditioning regimens activates host antigen-presenting cells, which then prime donor T cells leading to their expansion and differentiation, followed by a cytokine storm and target organ damage. This framework has been refined by recognition of the crucial role of the microbiome, innate lymphoid cells, regulatory T cells, and tissue-resident memory T cells in modulating GVHD development and severity. The role of the intestinal microbiome has received particular attention, with studies demonstrating associations between specific bacterial taxa and GVHD risk. Interventions including fecal microbiota transplantation have shown promise in pilot studies for steroid-refractory GVHD, with larger randomized trials ongoing.

The distinction between acute and chronic GVHD has evolved beyond the traditional 100-day boundary to encompass distinct clinical manifestations and underlying immunologic mechanisms. Chronic GVHD increasingly demonstrates features of immune dysregulation resembling autoimmune disorders, with involvement of B cells, TH17 cells, and aberrant fibrosis pathways. Recognition of the heterogeneity within both acute and chronic GVHD has prompted development of more refined classification systems that may better guide therapeutic approaches.

Standard GVHD prophylaxis has traditionally relied on Calcineurin Inhibitors (CNIs) combined with methotrexate or mycophenolate mofetil. However, this approach fails to prevent GVHD in many patients and carries significant toxicities. The incorporation of Anti-Thymocyte Globulin (ATG) has reduced chronic GVHD rates in multiple randomized trials, particularly in unrelated donor transplants, though questions remain regarding optimal dosing and impact on relapse risk. Post-Transplant Cyclophosphamide (PTCy) has emerged as a transformative approach allowing successful transplantation across HLA barriers. Initially developed for haploidentical transplantation, PTCy has expanded to matched unrelated and matched related donor settings with impressive reductions in severe acute and chronic GVHD compared to historical controls. The efficacy of PTCy appears to derive from selective depletion of alloreactive T cells while sparing regulatory T cells and stem cells.

Beyond these established approaches, several novel agents have shown promise in GVHD prevention. The proteasome inhibitor bortezomib demonstrated reduced acute GVHD rates in a phase 1/2 trial by targeting alloreactive T cells and antigen-presenting cells. JAK 1/2 inhibitors including ruxolitinib and itacitinib have shown efficacy in preventing GVHD in preclinical models and early clinical trials by blocking inflammatory cytokine signaling. The CCR5 antagonist maraviroc reduced visceral acute GVHD in a phase 1/2 study by inhibiting lymphocyte trafficking. Perhaps most promising is abatacept, a CTLA-4-Ig fusion protein that blocks T-cell costimulation. The phase 2 ABA2 trial demonstrated significantly reduced grades 3-4 acute GVHD with abatacept added to standard CNI-based prophylaxis, with a particularly striking impact on steroid-refractory GVHD.

For patients who develop acute GVHD despite prophylaxis, corticosteroids remain first-line therapy with complete response rates of approximately 50%. The management of steroid-refractory GVHD has been transformed by the approval of ruxolitinib based on the REACH2 trial, which demonstrated superior overall response rates compared to best available

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therapy (62% vs 39%). The survival benefit observed with ruxolitinib has established it as the standard second-line approach. Other agents showing promise in steroid-refractory acute GVHD include the IL-22 receptor agonist F-652, which demonstrated a 71% overall response rate in a phase 2 study, and vedolizumab, which targets the α4β7 integrin involved in gut-specific lymphocyte trafficking.