blood® Editorial

Introduction to a review series on strategies to improve GVL effects

Allogeneic hematopoietic cell transplantation (allo-HCT) is the only curative approach for a large group of hematological malignancies, and it relies heavily on graft-versus-leukemia (GVL) effects. Relapse or progression of the hematological malignancy is the leading cause of death after allo-HCT, indicating an unmet need to prevent relapse and induce remission when relapse occurs. For several decades, little progress has been made in treating relapsed patients. In the last 8 years, multiple novel immunotherapy approaches for relapse after allo-HCT have emerged. The following series of reviews describes the latest advances in relapse prevention and treatment including cellular therapies, antibody-based treatments, and tyrosine kinase inhibitor (TKI)–based approaches:

- Melody Smith, Johannes Zakrzewski, Scott James, and Michel Sadelain, "Posttransplant chimeric antigen receptor therapy"
- Sarah Cooley, Peter Parham, and Jeffrey S. Miller, "Strategies to activate NK cells to prevent relapse and induce remission following hematopoietic stem cell transplantation"
- Rupert Handgretinger and Karin Schilbach, "The potential role of γδ T cells after allogeneic HCT for leukemia"
- Robert J. Soiffer, Matthew S. Davids, and Yi-Bin Chen, "Tyrosine kinase inhibitors and immune checkpoint blockade in allogeneic hematopoietic cell transplantation"

The cellular therapy most frequently applied to treat post-transplant relapse are donor lymphocyte infusions (DLIs). Response rates vary depending on the underlying disease and remission status; they are highest in chronic myeloid leukemia but low in acute lymphoblastic leukemias (ALLs) and refractory non-Hodgkin lymphoma (NHL). For CD19-positive diseases (NHL and ALLs), the adoptive transfer of autologous T cells containing second-generation chimeric antigen receptors (CARs) targeting CD19 has been very successful in treating relapsed and refractory disease. Extending the application of CAR-targeted T cells to allo-HCT incurs the risk of graft-versus-host disease (GVHD). Smith et al review different approaches to overcoming this risk.

The review by Cooley et al discusses clinical strategies that enhance natural killer (NK) cell–based GVL effects via CD16-binding antibodies, modification of the preparatory regimen, and depletion of T regulatory cells by the interleukin-2 (IL-2) diphtheria toxin fusion protein denileukin diftitox (Ontak). NK cell survival and activation depend on the presence of IL-15; thus, IL-15N72D/IL-15Rα-Fc superagonist complexes and heterodimeric IL-15/IL-15Ra are currently undergoing clinical testing. Because NK cells are subject to immune escape mechanisms by leukemia cells, the combination of NK cells with immune checkpoint inhibitor antibodies directed against KIR, NKG2A, or Tim-3 is discussed, as well as the differential effectiveness of individual NK cell subsets.

Like NK cells, γδ T cells do not induce GVHD but can exhibit potent anti-leukemia effects in vitro. The review by Handgretinger et al describes the anti-leukemic properties of γδ T cells and how these properties can be exploited after allo-HCT in patients with leukemia. For instance, the combination of γδ T cells with antibodies containing binding sites for CD19 and CD16 was shown to mediate synergistic effects when combined with γδ T cells against CD19-positive leukemic blasts. Reconstitution of γδ T cells in pediatric patients with leukemia undergoing allo-HCT correlated with progression-free survival and overall survival as discussed by Handgretinger et al.

Although cellular therapies that rely on CAR technology or the ex vivo expansion of certain cell types (NK cells, γδ T cells) require time before the patient can be treated, drug-based approaches are directly available to the clinician who is often faced with patients experiencing rapidly progressing relapsed disease. TKIs directed at bcr-abl or fms-like tyrosine kinase 3 (FLT3), and immune checkpoint inhibitors against CTLA-4 and PD1 are particularly promising agents that are among the treatments discussed in the review by Soiffer et al. Preemptive strategies using imatinib, nilotinib, and dasatinib to prevent hematological relapse of bcr-abl–mutant hematological malignancies or sorafenib for FLT3-internal tandem duplication–mutant acute myeloid leukemia are discussed and placed into context with the literature on their mechanism of action. The currently available data on the 2 classes of checkpoint inhibitors (CTLA-4 and PD1) are also discussed, both alone and in combination with DLIs or hypomethylating agents.

This review series presents important insights into novel therapeutic strategies including cellular therapy approaches, immune checkpoint antibodies, and TKIs that have evolved during the past decade. A major goal of this review series is to provide the treating physician with an overview of novel therapeutic targets that have reached clinical testing and may change clinical care.

Robert Zeiser
Associate Editor, *Blood*

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