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Advancements in graft-versus-host disease prevention in hematopoietic stem cell transplantation

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Abstract:

Graft-versus-host disease (GVHD) remains a critical obstacle in the success of allogeneic hematopoietic stem cell transplantation (HSCT), adversely affecting patient survival and posttransplant quality of life. Recent advancements in GVHD prophylaxis emphasize achieving a delicate equilibrium between effective immunosuppression and preservation of the graft-versus-tumor (GVT) effect. This article synthesizes cutting-edge developments, including immune modulation strategies such as regulatory T-cell expansion and cytokine blockade, novel pharmacological approaches like Janus kinase inhibitors and posttransplant cyclophosphamide, and cellular therapies leveraging mesenchymal stromal cells and ex vivo-expanded regulatory T cells. Furthermore, the advent of biomarkers such as ST2 and microRNA signatures has enabled early risk stratification, fostering personalized, risk-adapted prophylactic strategies. By integrating these innovations, HSCT outcomes can be significantly improved, offering enhanced safety, reduced GVHD incidence, and optimized long-term patient care.

Keywords:

GVHD prevention, HSCT, immune modulation

Introduction

Hematopoietic stem cell transplantation (HSCT) remains a curative therapy for many hematologic malignancies, immune disorders, and inherited metabolic diseases.[1] However, graft-versus-host disease (GVHD), where the donor's immune cells attack the host's tissues, continues to be a life-threatening complication, significantly affecting posttransplant survival and quality of life. Recent advances in immune modulation, cell therapy, and precision medicine are transforming how we approach GVHD prevention, aiming to balance immunosuppression with maintaining the graft-versus-tumor (GVT) effect.[2,3] This article explores the latest developments in preventing GVHD and their potential to improve patient outcomes.

Immune Modulation Strategies in Graft-versus-host Disease Prevention

Immune modulation is at the forefront of GVHD prevention strategies, focusing on altering the host immune response without completely shutting it down. Regulatory T cells (Tregs), known for their ability to suppress immune reactions, have become a critical focus. Expanding Tregs in the donor graft or boosting their function in the recipient has shown promise in reducing GVHD incidence. By increasing the Treg population, immune tolerance toward host tissues can be enhanced, thereby reducing alloreactivity and preventing tissue damage.[4]

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Cytokine blockade is another approach in GVHD prevention. Pro-inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor-α, and IL-1 play a key role in GVHD development. Targeting these molecules with monoclonal antibodies has shown success in reducing the severity of both acute and chronic GVHD. These therapies can dampen the inflammatory response that triggers immune-mediated tissue damage while preserving other essential immune functions.[5]

In addition, selective depletion of alloreactive T-cells in donor grafts is being explored. Techniques such as CD3/CD19 depletion aim to remove harmful T-cell populations responsible for causing GVHD while sparing immune cells essential for pathogen defense and tumor surveillance. This method ensures that the graft retains its antitumor effect (GVT), vital in preventing relapse in patients with hematologic malignancies.[6]

Posttransplant Pharmacological Interventions

Pharmacological agents are pivotal in GVHD prevention, with the use of Janus kinase (JAK) inhibitors emerging as a novel therapeutic option. JAK inhibitors, such as ruxolitinib, have already been employed to treat steroid-refractory acute GVHD and are now being investigated for prophylactic use. These agents block critical signaling pathways involved in the immune response, reducing T-cell activation and cytokine production, thereby minimizing GVHD risk. Their use in prophylaxis could help patients who are unable to tolerate traditional immunosuppressants.[7]

One of the most exciting developments in pharmacological prevention is posttransplant cyclophosphamide. This therapy, initially developed for haploidentical (half-matched) transplants, has shown effectiveness in preventing GVHD in matched sibling and unrelated donor transplants as well. Administering cyclophosphamide early after transplantation selectively targets highly reactive donor T-cells that cause GVHD, while preserving T-cells critical for fighting infections and preventing cancer relapse. This method has revolutionized the safety and applicability of HSCT, especially for patients without fully matched donors.[8]

Cellular Therapies in Graft-versus-host Disease Prevention

In addition to pharmacological advances, cellular therapies have shown remarkable potential in preventing GVHD. Mesenchymal stromal cells (MSCs) are multipotent cells with anti-inflammatory and immunomodulatory properties, making them a promising option for GVHD prophylaxis. MSCs can be administered to the patient to regulate the immune response, reduce inflammation, and promote tissue repair in GVHD-affected organs. Early-phase clinical trials suggest that MSCs can reduce the incidence and severity of both acute and chronic GVHD, though further studies are needed to refine this approach.[9]

Another cutting-edge approach is the use of *ex vivo* expanded Tregs. Donor-derived Tregs, expanded in culture, can be infused into the recipient to suppress the activation of alloreactive T-cells that cause GVHD. By selectively enhancing the immune system's regulatory arm, Treg therapy can induce immune tolerance without compromising the ability to combat infections or cancer. Studies show that Treg infusion may reduce the need for prolonged immunosuppression and improve long-term transplant outcomes.[2,4]

Biomarkers for Predicting Graft-versus-host Disease

One of the key challenges in GVHD management is identifying patients at high risk before clinical symptoms arise. Recent research has focused on the development of biomarkers to predict GVHD risk, allowing for early and targeted intervention. Proteins such as ST2 and REG3α have been identified as potential biomarkers, correlating with GVHD severity. Elevated levels of these proteins in blood or serum samples can indicate a higher likelihood of developing severe GVHD, even before clinical signs appear.[10]

In addition, microRNA profiling has emerged as a promising tool in this area. MicroRNAs are small noncoding RNAs that regulate gene expression and can be used to detect immune dysregulation associated with GVHD. MicroRNA signatures in patient serum or tissue samples could help identify patients at risk and guide personalized prophylactic strategies, leading to better outcomes.[10]

Personalized Medicine and Risk-adapted Graft-versus-host Disease Prophylaxis

The advent of personalized medicine has led to risk-adapted strategies in GVHD prophylaxis, with a focus on tailoring treatments based on individual genetic and immunologic profiles. Genetic matching between donor and recipient, extending beyond traditional human leukocyte antigen (HLA) matching to include non-HLA markers such as minor histocompatibility antigens or killer immunoglobulin-like receptors (KIR), is becoming increasingly important. These additional genetic factors can influence GVHD risk and allow for better donor selection.[11]

In addition, personalized prophylaxis based on biomarker profiling allows for adjusting the intensity of immunosuppression according to a patient's risk level. High-risk patients may receive more aggressive prophylaxis, while those at lower risk can avoid overtreatment and its associated side effects, such as infections or delayed immune reconstitution.[10,11]

Conclusion

Prevention of GVHD remains a critical challenge in allogeneic HSCT, but recent advances in immune modulation, pharmacological interventions, cellular therapies, and personalized medicine offer promising strategies. By integrating these innovative approaches, it is possible to minimize the devastating effects of GVHD while maintaining the critical GVT effect. Ongoing research into novel biomarkers and risk-adapted prophylaxis will further refine GVHD prevention, enhancing the safety and efficacy of HSCT and improving long-term outcomes for patients undergoing this life-saving procedure.

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Conflicts of interest
There are no conflicts of interest.

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