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PROGRESS IN HEMATOLOGY

New immunotherapy-based approach in allogeneic hematopoietic stem cell transplantation

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a widely performed therapy for many hematologic malignancies. Recent progress with various sources of hematopoietic stem cells has enabled many more candidates to receive HSCT and a number of patients have now survived for years posttransplant. However, such patients still develop graft-versus-host disease (GVHD) and disease relapse are major causes of late death and morbidity. Now, several immunosuppressive agents are used for allogeneic transplantation recipients. However, therapeutic targets for GVHD, tumor and infection are overlapping and these immunosuppressive therapies are associated with increased relapse, impaired immune reconstitution, and more infections. In this review series, new immunotherapy-based approach in allogeneic HSCT, which are separating graft-versus-leukemia (GVL) effects and GVHD, are reviewed by experts. I believe this review series will deepen our understanding of transplantation immunology and recent progress in new immunotherapy-based therapy.

Regulatory T cells (Tregs) are pivotal for the maintenance of self-tolerance and tolerance induction after HSCT. Tregs suppress GVHD via early expansion of alloreactive T cell and cytokine dysregulation. And also Tregs are able to migrate into inflamed tissue and regulate the latter stage of immune responses. Although Tregs play an important role for the maintenance of peripheral tolerance and suppression of GVHD, Tregs do not inhibit cytotoxic T lymphocyte function against tumor and have little impact on GVL effects. Thus, Treg expansion after HSCT provides a promising strategy to treat GVHD. Matsuoka previously demonstrated that low-dose IL-2 administration was able to selectively stimulate Tregs and ameliorated the manifestations of chronic GVHD. In this review series, he will discuss current understanding of the polymorphic process of Treg reconstitution after HSCT and the appropriate intervention in the altered Treg homeostasis in each distinct reconstituting phase by low-dose IL-2 for better outcomes of patients after HSCT.

Schroeder et al. will present the evidence from studies regarding the use of hypomethylating agents (HMA), the FDA approved for the treatment of myelodysplastic syndromes after HSCT. And they also give an overview on potential mechanisms mediating the efficacy of HMA after HSCT. HMA have shown to upregulate several antigens on leukemic cells and seem to enhance T cell mediated antitumor activity by increasing tumor-specific CD8 T cell responses against these upregulated antigens. Moreover, HMA seem to interference with NK cell activity resulting to a HMA-mediated GVL effect. While, several studies reported that HMA induce the expression of Foxp3 in activated T cells generating functional Tregs with suppressor properties.

Van Elssen et al. will mainly focus on natural killer (NK) cell therapy after HSCT. NK cells are the most efficient effector cells of the innate immune system and have the capability to eliminate leukemic cells. In an experimental mouse model, NK cells have been shown to decrease GVHD after HSCT. They will present early clinical studies that demonstrate the safety of administration of ex vivo expanded NK cells after transplantation using feeder cells that express membrane-bound IL-21. And also they will discuss a therapeutic benefit in terms on decreasing relapse rate and possible control of viral infections after HSCT can be achieved.

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