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Hematopoietic stem cell therapy for autoimmune diseases – Clinical experience and mechanisms

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ABSTRACT

With accumulating evidence and improved outcomes along with recognition that modern biological therapies are not universally effective, require chronic administration and have high acquisition costs, hematopoietic stem cell transplantation (HSCT) has become an emerging direction for cell therapy in autoimmune diseases (ADs). The goal of this therapy is to induce medication-free remissions by resetting the immune system into a naïve and self-tolerant state through eradication of the autoreactive immunologic memory and profound re-configuration of the immune system induced by the transplant procedure. Safety of HSCT has generally improved by implementing internal quality management and external accreditation. Inter-disciplinary guidelines for patient selection, transplant technique and supportive care along with greater center experience should optimize safe and appropriate delivery of HSCT in specific ADs. In this review, we discuss the current role and future perspectives of HSCT in AD, focusing on recent published clinical and scientific studies and recommendations in the field.

1. Introduction

Autoimmune diseases (AD) are a heterogeneous group of conditions that affect around 10% of the population in Western countries with increasing incidence [1]. Such diseases constitute a heavy burden to society and are in many instances a debilitating health problem to the individual patient affected. AD are characterized by a breakdown of self-tolerance, triggered by certain environmental factors in a genetically predisposed population, with activation of normally quiescent autoreactive cells that escape self-regulation, resulting in chronic inflammation in target organs or multiple organ systems [2,3]. Although these conditions share common immunopathogenic mechanisms [4], the clinical phenotype widely varies depending on the type or tissue distribution of autoreactive clones involved.

Almost all current therapeutic concepts in AD are based on systemic suppression of immune functions, which ameliorate symptoms and halt progression in the vast majority of patients, but usually require continuous administration and may be associated with long-term side effects. Frequently, patients develop refractory disease states that are associated with significantly reduced quality of life and increased comorbidity.

The recent introduction of biologics, like cytokine blocking agents or B-cell depleting therapies, has added more specificity to an efficient disease management by targeted suppression of inflammation. It has become evident however, that only the eradication of the cells, secreting inflammatory mediators, rather than the blockade of secreted cytokines, will offer treatment-free remissions, i.e. cure. This therapeutic approach is based on the recent identification of an autoreactive immunologic memory as major driver of chronic autoimmune responses in ADs. Such memory cells, like long-lived plasma cells (PCs),

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are generated early during disease development and may even be present years before clinical symptoms occur [5]. They are harbored in dedicated survival niches in bone marrow or inflamed tissues, contributing to chronic autoimmune responses by the continuous secretion of autoantibodies, but are unresponsive to state-of-the-art immunosuppressive as well as targeted B-cell therapies [6,7].

Alternative cellular therapies have, therefore, emerged to reset or rebalance the immune system to restore self-tolerance. Among those, hematopoietic stem cell transplantation (HSCT) following high dose chemotherapy has developed as a promising treatment option for patients with ADs responding poorly or refractory to conventional treatments [8]. In this review, we summarize the clinical experience accumulating over the past 20 years and highlight most relevant mechanistic studies unraveling the immunological mechanisms of HSCT in various ADs.

2. Rationale and preclinical models of HSCT for autoimmune diseases

Hematopoietic stem cell transplantation (HSCT) is a standard of care for hematological malignancies and congenital or acquired disorders of the hematopoietic system yielding at eradication of malignant cell clones by a conditioning regimen, usually a combination of chemotherapy agents, with or without radiation therapy, salvaged by transplantation of hematopoietic stem cells (HSC) previously isolated from the bone marrow (Fig. 1). The source of HSC can either be autologous, which allows the administration of high-dose chemotherapy without prolonged bone marrow aplasia or allogeneic, which is associated with the risk of graft versus host disease (GvHD) but has the advantage of providing alloimmunity with graft-versus-tumor effect to eradicate residual disease.

The experimental basis for the treatment of AD with HSCT derives from the pioneering translational research in murine models of autoimmunity of Ikehara in 1985, who first evidenced that the origin of autoimmune diseases is in the bone marrow and that bone marrow and not thymus transplantation can restore tolerance [9]. Subsequently, van Bekkum and co-workers demonstrated that conditioning followed by transplantation of syngeneic (i.e., pseudoautologous) HSC resulted in cure of induced models of autoimmunity, in particular collagen-induced arthritis (CIA, a model for rheumatoid arthritis, RA) and experimental autoimmune encephalomyelitis (EAE, as model for MS), suggesting that tolerance induced by HSCT can prevent autoimmunity even after antigenic re-encounter [10–12]. Similar results were obtained in models of spontaneous (i.e., genetically determined) AD, such as lupus-prone mice, where both allogeneic and syngeneic HSCT could induce prolonged remissions [13].

In human autoimmunity, the role of genetic predetermination in disease development is still uncertain. Although varying across different ADs, genome wide association studies (GWAS) as well as twin studies indicated that genomic variants predispose to autoimmunity, but environmental factors seem to have a major impact in disease development [14,15], suggesting that autologous HSCT may potentially provide a curative treatment option in ADs. This notion is supported by serendipitous case reports demonstrating that patients with coincident autoimmune disease and hematological malignancy may remain in long-term remission of both diseases after autologous HSCT [16–18].

3. Proposed mode of action of HSCT in autoimmune diseases

Early pilot trials in severe forms of AD, including multiple sclerosis (MS), systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis (JIA), demonstrated that autologous HSCT could induce sustained treatment-free remissions, confirming the potential benefits of this type of stem cell therapy in appropriately selected patients [19–21]. Meanwhile, considerable advances were made in understanding the mode of action of HSCT. Mechanistic studies demonstrated that HSCT exerts not only prolonged downstream immunosuppressive effects, but also induces fundamental changes in chronically dysfunctional immune systems, restoring a naïve and self-tolerant state [8,22,23]. Such ‘re-booting’ of self-tolerance is achieved through two principal pathways: (i) purging of the pathogenic autoreactive immune repertoire and (ii) profound immunologic renewal, i.e. immune reset (Fig. 2).

By analogy to HSCT for hematologic cancers (with eradication of malignant clones), immunoablation for ADs is performed on the premise of removal of autoreactive immunologic memory cells. This notion is supported by serologic data and T-cell receptor (TCR) repertoire analyses demonstrating disappearance of pre-existing serum autoantibodies [24] and prominent T-cell clones [25,26] post-transplantation, respectively. Further studies of immune reconstitution have provided evidence for substantial post-transplant modification of the adaptive immune system in various AD, including a vast diversification of the TCR repertoire [25,27,28] and functional renewal of the T regulatory (Treg) cell compartment [29–31].

Immune reconstitution occurs at different paces in different lineages and subsets (Fig. 1). Following engraftment, the first phase of immune reconstitution is characterized by a significant though transient increase in the proportion of natural killer (NK) cells and clonal expansion of residual memory T-cells due to antigen encounter during early infections or driven by lymphopenia-induced homeostatic proliferation. Subsequently, regeneration of a new, naïve T- and B-cell repertoire occurs, emerging from thymic reactivation, which represents a form of

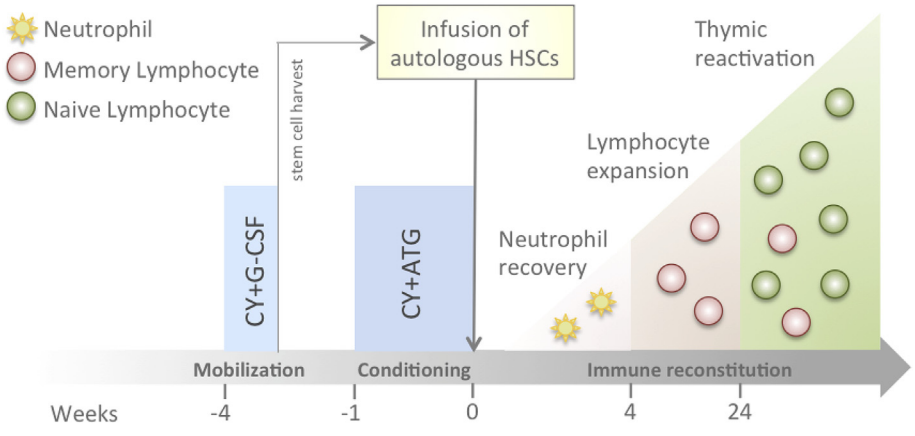

Fig. 1. Hematopoietic stem cell transplantation in patients with autoimmune disease. Autologous hematopoietic stem cells (auto-HSC) are harvested from peripheral blood, purified (mostly using CD34 selection with magnetic separation) and cryopreserved after being mobilized from bone marrow by treatment with cyclophosphamide (CY) and granulocyte colony stimulating factor (G-CSF). Approximately 4 weeks later patients receive a conditioning to eradicate autoreactive immunologic memory cells, usually a combination of intravenous CY and anti-thymocyte globulin (ATG). Subsequently, HSC are infused to allow the regeneration of a new immune system that is reset to a self-tolerant state. After engraftment and neutrophil recovery, the first phase of immune reconstitution is characterized by clonal expansion of residual memory lymphocytes in response to early infections and/or lymphopenia-induced proliferation. Finally, lymphocyte renewal occurs through thymic reactivation leading to restoration of a polyclonal repertoire of T regulatory and conventional T-cells.