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General review

Resetting the immune response after autologous hematopoietic stem cell transplantation for autoimmune diseases

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ABSTRACT

Autologous hematopoietic stem cell transplantation (AHSCT) is currently investigated as treatment for severe and refractory autoimmune diseases, such as multiple sclerosis (MS), systemic sclerosis (SSc), Crohn's disease (CD) and systemic lupus erythematosus. Randomized clinical trials in MS, SSc and CD have shown the efficacy of AHSCT to promote control of disease activity and progression, when compared to conventional treatment. The use of high dose immunosuppressive conditioning is essential to eliminate the autoimmune repertoire, and the re-infusion of autologous hematopoietic stem cells avoids long-term leucopenia by reconstitution of both immune and hematological systems. Recent studies showed that AHSCT is able to deplete the autoimmune compartment and further promote the formation of a new autotolerant immune repertoire, reducing the inflammatory milieu and leading to long-term clinical remission without any complementary post-graft treatment. Deep knowledge about the mechanisms of action related to AHSCT-induced remission is required for the management of possible post-AHSCT relapse and improvement of clinical protocols. This paper will review the mechanisms enrolled in the immune response resetting promoted by AHSCT in patients with autoimmune diseases.

1. Introduction

Autologous hematopoietic stem cell transplantation (AHSCT) is an alternative treatment for patients with severe autoimmune disease (AD) refractory to conventional treatments [1]. This innovative therapy has been used to treat several AD, such as neurological disorders (multiple sclerosis), connective tissue diseases (systemic sclerosis and systemic lupus erythematous), gastrointestinal inflammatory diseases (Crohn's disease) and others (juvenile arthritis, type 1 diabetes and hematologic immune cytopenia) [2]. Experience in phase I–II clinical trials over the years [3–14] and more recently on randomized phase II–III clinical trials [15–17] has led to increased safety and efficacy of the procedure, besides improving patients' quality of life, functional status and overall/event-free survival [2,18]. Recent studies have demonstrated superior therapeutic efficacy of AHSCT *versus* conventional therapies [15–17], showing that transplantation can induce long-term disease stabilization in the absence of any further complementary treatment post-therapy. Therefore, this approach has been increasingly accepted for its combination of safety and efficacy [2,19–21]. These investigations contributed to improve the clinical management and both EMBT [1] and CIBMTR guidelines have been updated to refine patient selection and transplantation protocols, aiming to further enhance transplant outcomes in clinical practice [22].

The management of AHSCT can be divided in four parts:

- mobilization of hematopoietic stem cells (HSCs) from bone marrow to peripheral blood using chemotherapy (usually low doses of cyclophosphamide and G-CSF);
- HSCs apheresis with or without $CD34^+$ selection;
- conditioning phase with high doses of immunoablative drugs, as cyclophosphamide, anti-thymocyte globulin, fludarabine or

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other chemotherapies, with or without the addition of monoclonal antibodies;
- infusion of the previous collected autologous HSCs [23].

The rationale involves non-specific abrogation of autoreactive T- and B-cell responses by the use of high dose immunosuppression (HDI) during conditioning, interrupting the autoimmune aggression, and successful reconstitution of a new and tolerant immune system by the re-infusion of the HSCs [24–27].

The concept of "immune resetting" after AHSCT has been proposed, and is currently defined as the eradication of an existing immune system, which is replaced by a new immune repertoire, associated with re-instatement of appropriate immune regulation. These three well-defined mechanisms of immune resetting may be synergistic and their relative contribution to disease control may depend on the transplantation regimen and on the underlying disease [23–29].

Despite increased experience in the use of AHSCT to treat AD, some patients may remain not fully responsive or even be completely unresponsive to the therapy according to the type and severity of AD at the time of inclusion [2]. In this context, detailed evaluation of the newly reconstituted immune system after AHSCT is essential to clarify the underlying mechanisms of the expected immune resetting and allow the identification of biomarkers of response, which are necessary to improve clinical protocols and promote a greater application of this therapy in the treatment of these diseases. In the following sections, we review the reset of immune response and clinical remission induced by AHSCT in severe ADs patients.

2. Depletion of the autoimmune repertoire

ADs are triggered by the loss of immunological tolerance, with an exacerbated activation of the adaptive immune system leading to tissue damage [30]. Several factors are involved in the development of ADs, such as the over-activation of autoreactive T- and B-cells and reduced immunoregulatory capacity of Tregs, in patients with predisposing genetic background [30,31]. To induce clinical remission, AHSCT should efficiently deplete the autoimmune repertoire, enabling the installation of a new and autotolerant immune system. In addition, an improved immunoregulatory network is expected, via the generation of Tregs with suppressive functions as well as the residual autoreactive cells reprogramming towards a more anti-inflammatory phenotype [24,32,33] (Fig. 1).

Multiple sclerosis (MS) is characterized by the autoimmune inflammatory reactions in the central nervous system, resulting in axonal demyelination due to T- and B-cells activation against several components of brain tissue [34]. Complete abrogation of baseline autoreactivity after transplantation was recently described in MS patients, as measured by antigen-specific $CD4^+$ and $CD8^+$ T-cells proliferative responses to myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG) and proteolipid protein peptide (PLP) [35]. These results were confirmed by an independent group, who showed that MBP-reactive T-cells were depleted and remained low in frequencies until 9 months post-AHSCT in four MS patients [36].

In systemic sclerosis (SSc) patients, the endothelial vascular damage as consequence of early T-cell activation, production of autoantibodies by autoreactive plasma cells (remarkably anti-topoisomerase-I) and of fibroblasts pro-fibrotic cytokines aberrant secretion are the disease hallmarks [37]. Several studies also demonstrated the reduction of autoimmunity after AHSCT in SSc patients. In a French cohort of 7 patients, reduction in the anti-topoisomerase (anti-Scl-70) autoantibody levels post-transplantation was achieved in all patients [38]. The decrease was more prominent in the good clinical responders ($n = 4$) and high $CD19^+$ and $CD20^+$ B-cell counts positively correlated with anti-Scl-70 levels, suggesting that pathogenic B-cell clones might preferentially expand in the patients with a less favorable outcome [38]. Such observation was confirmed in two other studies, with progressive decrease in the anti-Scl-70 autoantibodies in 11 SSc patients over 3 years follow-up [39], and a specific reduction of anti-Scl-70 titers in 9/10 transplanted patients, while the total gamma-globulin serum levels remained within normal range post-AHSCT [40].

Systemic lupus erythematosus (SLE) is characterized by the B-cell hyper-responsiveness and chronic autoreactive plasma cells activation with consequent secretion of autoantibodies against several antigens, mainly nuclear contents [41]. In SLE patients, high serum titers of anti-double-stranded DNA and of antinuclear antibodies (ANA) decreased significantly after AHSCT, correlating with clinical remission [42]. These alterations were triggered by changes in the B-cells compartment. After AHSCT, there is strong reduction of $CD19^+$ IgD^- memory B-cell counts, as well as of the $CD20^-$ $CD27^{high}$ plasmablasts, followed by predominant reconstitution of $CD19^+$ IgD^+ naive B-cells. However, the non-specific depletion imposed by HDI also eliminates memory B-cells of all specificities, leading to loss of protective antibodies. Serum antibodies specific for measles, mumps, tetanus and diphtheria became non-detectable in the immunoablated patients, in parallel

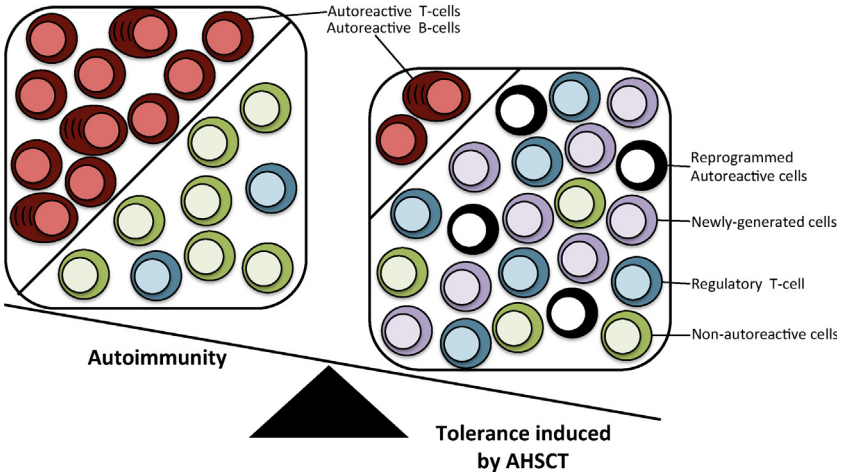

Fig. 1. Possible mechanisms enrolled in AHSCT-induced tolerance. Transplantation of AHSC re-shapes the immunologic system due the depletion of the autoreactive T- and B-cells, followed by the immune repertoire renewal trough the *de novo* generated thymic-derived naive T-cells exportation and expansion of regulatory T-cells, as well by the reprogrammation of the non-depleted autoimmune cells from a pro-inflammatory autopathogenic profile to an auto-tolerant one.