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REVIEW

Hematopoietic and mesenchymal stem cell transplantation for severe and refractory systemic lupus erythematosus

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Abstract Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by multi-organ involvement leading to significant morbidity and mortality in predominantly young women. The underlying pathogenesis involves the emergence of autoreactive T and B lymphocytes, production of autoantibodies, formation and deposition of immune complexes in various tissues leading to inflammation and organ damage. Recently, growing evidence suggests that the functions of hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) are disrupted in SLE pathology. And HSC or MSC transplantation (HSCT/MSCT) can offer an effective and safe therapy for the severe SLE patients, resulting in disease clinical remission and improvement of organ dysfunction. In this article, we provide a brief overview of current research of autologous or allogeneic HSCT/MSCT in SLE and describe our current understanding of the mechanisms by which it plays a part in treating SLE, for better understanding of the pathogenesis, diagnosis and treatment for SLE.

Contents

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystemic autoimmune disease that involves multiple organs including renal, cardiovascular, neural, musculoskeletal, and cutaneous systems and remarkable variability in clinical presentation. The pathogenesis of SLE is complex [1], which resides in a complex interplay of genetic, endogenous (including hormonal), and environmental stimuli, resulting in a breakdown of self-tolerance and development of autoimmunity with organ damage [2]. Major organ manifestations, particularly central nervous system and renal disease, have long been identified as markers of poor prognosis [3,4]. The most widely and classically used immunosuppressive therapies, notably corticosteroids and cyclophosphamide (CYC), have led to a significant improvement in survival over the last few decades and decreased the progression to end-stage multiorgan failure. However, the usage of these medications often results in serious side-effects such as infection, ovarian failure and secondary malignancy [5–7], and the disease often relapses after drug-withdrawl [8], which remains important causes of mortality in SLE patients. In addition to conventional medical therapies, several new strategies have been developed targeting specific signaling pathways with small molecules and biological agents [9–12]. For instance, B-cell-depleting therapies using the monoclonal antibodies rituximab, ocrelizumab, epratuzumab, and belimumab have benefitted a specific subpopulation of lupus patients [13–15]. However, the prolonged administration of these therapies is expensive. Therefore, it is urgent to develop amore effective therapy for SLE, especially for those who are refractory to treatment.

In recent years, several studies suggest that autoimmune diseases including SLE may be identified as a stem cell disorder as evidenced by direct disease transfer to recipients of allogeneic HSC transplantation from diseased donors [16,17] as well as in animal models [18]. In addition, the etiopathogenesis of SLE is attributable to defects in the bone marrow microenvironment, mainly in the hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) [19]. As adult somatic stem cells, HSCs and MSCs are multipotent, and unlike ESCs, their acquisition is not associated with ethical issues for they do not develop into teratomas. Evidence has suggested that HSCs/MSCs from patients with systemic lupus erythematosus (SLE) exhibited impaired proliferation, differentiation, and immune modulation capacities. Based on this finding, the new cell-based therapeutic approach appears as a promising therapy for SLE disorder, especially for treatment-refractory patients. Indeed, for SLE, both animal experiments and clinical trials have shown that HSCT/MSCT results in amelioration of disease activity, improvement in serologic markers, and either stabilization or reversal of organ dysfunction. In the present article, our aim is to discuss recent progress in understanding the role of malfunctioning HSC/MSC in etiopathogenesis of SLE and to explore autologous or allogeneic HSCT/MSCT as a potential therapy for SLE.

2. SLE is a HSC/MSC disorder

Bone marrow-derived mesenchymal stem cells (MSCs) are key components of the hematopoietic microenvironment and provide support to hematopoiesis and modulate immune system. However, evidence has suggested that bone marrow mesenchymal stem cells (BMSCs) from patients with systemic lupus erythematosus (SLE) exhibited impaired capacities of proliferation, differentiation, secretion of cytokines and immune modulation. Sun et al. [20–23] studied the biological character of bone marrow derived MSCs in patients with SLE, focused on their phenotype (morphology and immunophenotype), karyotype, cytokine expression and hematopoietic support of MSCs. They found that MSCs from SLE patients and normal controls can be successfully culture-expanded, but the MSCs from SLE grew more slowly than those of normal controls ($p < 0.05$). Normal BM-MSCs can be cultured for 40 passages without losing their productive motility. In contrast, BM-MSCs from SLE patients can only be cultured for about 10 passages, after which the culture shows senescence behavior [20]. MSCs from SLE have a normal karyotype, cells from both groups were positive for CD29, CD44 and CD105, and negative for CD14, CD34, CD45 and HLA-DR. However, MSCs from patients with SLE compared to controls were defective in secreting cytokines (i.e., transforming growth factor β) accompanied by down-regulation of interleukin 6 (IL-6) and IL-7 mRNA expression [20], that abnormality of cytokine secretion may lead to hematopoiesis damage and immune imbalance. They also observed that the cytoskeleton and ultra-structure of SLE BM-MSCs are abnormal, for instance, lots of autophagosome were found in majority of cells, F-actin was confused and dense on the edge of cytoplasm. Vinculin was disordered and dense on the cytoplasm [21]. The changes of ultrastructure and cytoskelet on in MSC from SLE may play an important role in its being incapable of cell expansion in vitro. Their findings also showed that the