Autologous hematopoietic stem cell transplantation in the treatment of severe autoimmune disease

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Abstract

Some of patients with autoimmune disease (AD), having progressive skin sclerosis or interstitial pneumonia (IP) etc., are severely damaged or fatal from the treatment-resistant disease progression. To induce remission in such severe AD by eradication of autoreactive lymphocytes and by immune reconstitution, we underwent a phase I-II trial to elucidate feasibility and efficacy of autologous hematopoietic stem cell transplantation (auto-HSCT) for severe AD. Nineteen patients with systemic sclerosis (SSc), 3 patients with dermatomyositis and a patient with Wegener’s granulomatosis (WG) were enrolled. Peripheral blood stem cells (PBSCs) were mobilized with cyclophosphamide (CY, 4 g/m²) and G-CSF. After collecting PBSCs more than 2x10⁶ CD34+ cells/kg by apheresis, they were cryopreserved until autografting. CD34+ cells were immunologically selected in 11 SSc patients, 2 dermatomyositis patients and a WG patient just after apheresis. All of the patients were treated with high-dose CY (200 mg/kg) and received auto-HSCT. There was no treatment-related mortality. As toxicity, there were a variety of post-transplant infections such as adenoviral hemorrhagic cystitis, herpes zoster, and cytomegaloviral antigenemia. In patients with SSc, skin sclerosis was markedly improved in all of the patients within 6 months and the improvement was sustained for 60 months after auto-HSCT. Vital capacity was significantly increased at 48 months after HSCT and KL-6, a marker for IP, was significantly decreased during 12-60 months after HSCT. A titer of anti-Scl-70 was significantly decreased during 1-60 months after HSCT. Progression-free and overall 5-year survivals were 66% and 93%, respectively. In patients with dermatomyositis, progressive IP and skin ulcers were dramatically improved after auto-HSCT. In a patient with WG, the size of the left orbital granuloma decreased. To study the mechanism for durable effects, we analyzed the immune reconstitution after HSCT in 11 SSc patients with CD34+ selection. The number of CD8+ T cells recovered as fast as a month, in contrast, that of CD4+ T cells was severely suppressed for 60 months after HSCT. The number of CD4+CD45RO+ memory T cells recovered earlier than those of CD4+CD45RA+ naïve T cells. The number of B cells recovered to the baseline at 12 months after HSCT. Of note, CD4+ Th1 cells became predominant, and Th1/Th2 ratio was significantly increased during 1-60 months after HSCT. CD34-selected auto-HSCT was more effective on skin sclerosis and was more strongly associated with viral infection than unmanipulated auto-HSCT. In conclusion, auto-HSCT is feasible and effective in the treatment of severe AD.