pISSN: 2093-940X, eISSN: 2233-4718
Journal of Rheumatic Diseases Vol. 24, No. 4, August, 2017
https://doi.org/10.4078/jrd.2017.24.4.171

Editorial

Autologous Haematopoietic Stem Cell Transplantation for Refractory Rheumatic Diseases

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Recently Lee et al. [1] published an interesting article that the long-term outcomes of autologous peripheral blood stem cell transplantation (PBSCT) to treat refractory rheumatic diseases. They assessed 11 Korean patients who underwent PBSCT for refractory rheumatic diseases between 2002 and 2005 for outcomes including treatment response, adverse events, damage accrual, and survival. Overall 10-year survival rate was 70% with a 40% recurrence rate and 20% treatment-related mortality rate. Their overall prognosis was not substantially different from previous reports [2-4].

Hematopoietic stem cell transplantation (HSCT) has been proposed as an effective alternative treatment for refractory rheumatic diseases. The first treatment with autologous HSCT in a patient with rheumatic disease was described in 1996 [5]. Following the study, further autologous HSCT were performed, many under the framework of the European Society for Blood and Marrow Transplantation (EBMT)/European League Against Rheumatism autoimmune disease stem cell project [6]. The EBMT registry now comprises over 1,800 HSCT procedures performed to treat severe rheumatic diseases, including systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis, juvenile idiopathic arthritis, and Sjögren's syndrome [7]. The aim of HSCT in autoimmune disease is the eradication of autoreactive immune cells and the regeneration of a naive, self-tolerant immune system [8]. To date, a variety of mechanisms have been proposed to explain the clinical effects ("immune reboot") of autologous HSCT in severe autoimmune diseases. Whereas a "debulking of inflammation" is an instantaneous and predictable effect of any high-dose cytotoxic conditioning regimen, sustained clinical responses are best explained by long-term alterations in immune reconstitution via thymic and/or extrathymic pathways. Shifts in T- and B-cell subpopulations from memory to naive cell dominance, with restoration of polyclonal T-cell receptor (TCR) diversity, correction of immune gene expression abnormalities, and other changes in T cells, B cells, plasmablasts, and natural killer cells support immune re-education and tolerization with autologous HSCT [9]. HSCT renews the CD4+ T cell compartment and the Treg cell population, which is accompanied by an increase in the number of Treg cells and the re-establishment of TCR diversity and function. The thymus is likely to have an important role in restoring this immune balance. Also, following transplantation, the B cell compartment becomes naive and the number of autoreactive antibodies decreases [7]. Clinical remission in autoimmune disease after HSCT is the result of a true reconfiguration of the immune system instead of long-term immunosuppression.

There is now sufficient evidence that HSCT can result in significant improvement of skin thickness and functional ability in SSc [10], while the recently completed Autologous Stem Cell Transplantation International Scleroderma trial demonstrated that HSCT can also prolong survival in selected patients with diffuse cutaneous SSc when compared with IV pulse cyclophosphamide [11]. In patients with SSc, autologous HSCT results in increased treatment-related mortality within the first year but a considerable long-term, event-free survival benefit

Received : August 14, 2017, **Accepted :** August 16, 2017

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afterwards.

One hundred fifteen autologous HSCTs for SLE have been reported to EBMT registry to date [12] since its first application in 1997 [13]. The two largest experiences so far come from the EBMT data registry (n=85; mean follow-up: 25 months, range: 2～123 months) [14] and from the single center pilot trial by Northwestern University (n=50; mean follow-up: 29 months, range: 6～90 months) [4]. The probability of five-year disease free survival was 50% in both studies, similar to results from smaller pilot studies [15]. Meanwhile, mechanistic studies have provided the proof of-concept that autologous HSCT not solely acts as prolonged immunosuppression, but rather rewires an autoreactive immune system into a self-tolerant state. This is achieved by two major principles; i) vast eradication of the autoreactive immunologic memory by an immunoablative regimen and ii) fundamental reconfiguration of the adaptive immune system [12]. This notion is reflected by a significant decrease or even disappearance of autoantibody levels (including anti-dsDNA, anti-phospholipid and antinuclear antibodies), where chronic immunosuppression had been ineffective.

Autologous HSCT is worth emphasizing in terms of its curative potential for treatment. The advantage of autologous HSCT is the almost complete ablation of the autoreactive memory for the resetting of the immune system becoming tolerant to self that can provide sustained remission in the absence of chronic immunosuppression [12]. Compared to continued insufficient or failed chronic immunosuppression, early use of autologous HSCT has the potential to protect against organ-failure and toxicity-related morbidity, improve quality of life and reduce socioeconomic costs.

However, autologous HSCT requires a careful selection of patients according to rheumatic diseases, consideration of therapeutic alternatives, risks and benefits, and the expertise of the transplantation team. The results of autologous HSCT depend on better patient selection, center effect, transplantation early in the disease course and preemptive infection and other supportive therapies.

In addition to autologous HSCT, mesenchymal stem cells (MSCs), might also have potential for rheumatic disease treatment. MSCs have potent immunoregulatory and anti-inflammatory properties. The relative ease of harvesting MSCs and their stable phenotype in culture make the cells an attractive tool for cellular therapy in alloimmunity, autoimmunity, and inflammation [16]. This phenomenon has led to an increasing number of clinical trials. Recently clinical trials with this goal are ongoing in patients with rheumatic diseases. Further studies are necessary to ascertain the concept of MSCs in order to establish the treatment strategy for use in rheumatic diseases.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Lee S, Bae SC, Jun JB, Choi CB. Long-term outcomes of autologous peripheral blood stem cell transplantation for refractory rheumatic diseases. J Rheum Dis 2017;24:149-56.
2. Snowden JA, Pearce RM, Lee J, Kirkland K, Gilleece M, Veys P, et al. Haematopoietic stem cell transplantation (HSCT) in severe autoimmune diseases: analysis of UK outcomes from the British Society of Blood and Marrow Transplantation (BSBMT) data registry 1997-2009. Br J Haematol 2012;157:742-6.
3. Snowden JA, Saccardi R, Allez M, Ardizzone S, Arnold R, Cervera R, et al. Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 2012;47:770-90.
4. Burt RK, Traynor A, Statkute L, Barr WG, Rosa R, Schroeder J, et al. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. JAMA 2006; 295:527-35.
5. Tamm M, Gratwohl A, Tichelli A, Perruchoud AP, Tyndall A. Autologous haemopoietic stem cell transplantation in a patient with severe pulmonary hypertension complicating connective tissue disease. Ann Rheum Dis 1996;55:779-80.
6. Tyndall A, Gratwohl A. Blood and marrow stem cell transplants in auto-immune disease: a consensus report written on behalf of the European League against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 1997; 19:643-5.
7. Swart JF, Delemarre EM, van Wijk F, Boelens JJ, Kuball J, van Laar JM, et al. Haematopoietic stem cell transplantation for autoimmune diseases. Nat Rev Rheumatol 2017; 13:244-56.
8. Alexander T, Bondanza A, Muraro PA, Greco R, Saccardi R, Daikeler T, et al. SCT for severe autoimmune diseases: consensus guidelines of the European Society for Blood and Marrow Transplantation for immune monitoring and biobanking. Bone Marrow Transplant 2015;50:173-80.
9. Snowden JA. Rebooting autoimmunity with autologous HSCT. Blood 2016;127:8-10.
10. van Laar JM, Naraghi K, Tyndall A. Haematopoietic stem cell transplantation for poor-prognosis systemic sclerosis. Rheumatology (Oxford) 2015;54:2126-33.
11. van Laar JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical

trial. JAMA 2014;311:2490-8.
12. Alexander T, Hiepe F. Autologous haematopoietic stem cell transplantation for systemic lupus erythematosus: time ready for a paradigm shift? Clin Exp Rheumatol 2017;35: 359-61.
13. Marmont AM, van Lint MT, Gualandi F, Bacigalupo A. Autologous marrow stem cell transplantation for severe systemic lupus erythematosus of long duration. Lupus 1997;6:545-8.
14. Jayne D, Passweg J, Marmont A, Farge D, Zhao X, Arnold R, et al. Autologous stem cell transplantation for systemic lupus erythematosus. Lupus 2004;13:168-76.
15. Alexander T, Arnold R, Hiepe F. Autologous hematopoietic stem cell transplantation in systemic lupus erythematosus. Z Rheumatol 2016;75:770-9.
16. Le Blanc K, Mougiakakos D. Multipotent mesenchymal stromal cells and the innate immune system. Nat Rev Immunol 2012;12:383-96.