

Autologous Stem Cell Transplantation in the Treatment of Refractory Rheumatoid Arthritis

The concept of using high-dose immunosuppressive treatment (HDIT) with autologous stem cell transplantation (ASCT) to treat patients with refractory rheumatoid arthritis has been provided by animal studies and anecdotal case reports. Over the past five years, an increasing number of patients with refractory rheumatoid arthritis have received HDIT with ASCT as an adjunct to intense immunosuppression. Here, we present a case of refractory rheumatoid arthritis in a 54-yr-old woman using HDIT with ASCT. Peripheral blood stem cells were mobilized with cyclophosphamide (4 g/m²) followed by G-CSF (5 µg/kg/day). Leukapheresis continued daily until the number of harvested progenitor cells reached 2×10^6 CD34+ cells/kg after CliniMax[®] CD34+ positive selection. For HDIT, high-dose cyclophosphamide (total dose 200 mg/kg) and antithymocyte globulin (total dose 90 mg/kg) were administered and CD34+ cells were infused 24 hr after HDIT. The patient tolerated the treatment well but experienced an episode of neutropenic fever. She achieved an early dramatic improvement of joint symptoms during therapy. Fifty percent of improvement of rheumatoid arthritis by the American College of Rheumatology (ACR 50) preliminary definition was fulfilled during the 6 months following ASCT. Although further long-term follow-up is required, the patient's activity of arthritis has been stable since receiving HDIT with ASCT.

Key Words : Cell Transplantation; Arthritis, Rheumatoid; Transplantation, Autologous

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INTRODUCTION

It has recently been suggested that high-dose immunosuppressive treatment (HDIT) with autologous stem cell transplantation (ASCT) can be an alternative therapeutic modality for the management of severe autoimmune diseases (1-5). Rheumatoid arthritis (RA) is one of the most common systemic autoimmune diseases in which morbidity is substantial and current treatment often remains unsatisfactory. Therefore, refractory RA has been regarded as a possible candidate for HDIT with ASCT (6-9). Here, we report a case of HDIT with ASCT in the treatment of 54-yr-old patient with refractory RA.

CASE REPORT

A 54-yr-old woman had been suffering from erosive, seropositive, polyarticular rheumatoid arthritis for 10 yr, which was resistant to available antirheumatic agents. She had previously been treated unsuccessfully with each of the following disease-modifying antirheumatic drugs (DMARDs): hydroxychloroquine (HCQ, 400 mg/day), methotrexate (MTX,

17.5 mg/week), sulfasalazine (SSZ, 2.0 g/day), and bucillamine (200 mg/day). She also underwent multiple combination therapy (HCQ+SSZ+MTX), but she did not receive cyclosporin due to severe gastrointestinal discomfort. She had also been treated with concomitant use of glucocorticoids, which was ineffective. The patient underwent right shoulder and left elbow replacements for the complications resulting from RA. Multiple intraarticular glucocorticoid injections were made, but no significant improvement was noticed throughout the entire disease course. On first admission, her Ritchie Articular Index (RAI) was 26. The number of tender joints (68 joints total) and swollen joints (66 joints total) was 27 and 22, respectively. The patient's global assessment of disease status was 95% (0% is best and 100% is worst). The physician's global assessment of disease status was 85% (0% is best and 100% is worst). The patient's assessment of physical function according to the Korean Health Assessment Questionnaire (KHAQ) was 3.2 (10). The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were 3.63 mg/dL and 32 mm/hr, respectively. Other laboratory findings were as follows: leukocyte 6,100/µL, hemoglobin 12.3 g/dL, hematocrit 38.4%, platelet 304,000/µL, total protein 6.6 g/dL, albumin 3.5 g/dL, creatinine 0.8 mg/dL, ALT/

AST 10/14 IU/L, and rheumatoid factor 161 IU/L.

The protocol was approved by the Institutional Review Board of HUKH (Hanyang University Kuri Hospital, Korea) and the patient provided written informed consent.

Peripheral blood stem cells were mobilized with cyclophosphamide (CTX, 4 g/m²), followed by granulocyte-colony stimulating factor (G-CSF, 5 µg/kg/day). Leukapheresis was initiated on day 12 when the leukocyte count was above 1,000/µL by CS3000® (Baxter, U.S.A.) for 2 days until CD34+ cells reached 2 × 10⁶ cells/kg. For CD34 positive selection, the CliniMax® column (Am Cell Corporation, Sunnysvale, U.S.A.) was used. A month after leukapheresis, the patient was readmitted to undergo autologous stem cell transplantation (ASCT). Cyclophosphamide (total dose 200 mg/kg) was administered in doses of 50 mg/kg/day intravenously for 4 days. Antithymocyte globulin (ATG, total dose 90 mg/kg) was infused at a doses of 30 mg/kg/days. Methylprednisone was administered intravenously for 30 min before each dose of ATG. Forty-eight hours after HDIT, stored CD34+ stem cells were infused via central route and G-CSF (5 µg/kg/day) was administered subcutaneously until the absolute neutrophil count was greater than 1,000/µL for 3 consecutive days. The numbers of infused CD34+ cells were 2.12 × 10⁶ cells/kg. The patient tolerated relatively well to the treatment with WHO grade II nausea, vomiting, and skin

rash. An episode of neutropenic fever was controlled with empirical antibiotics. The patient achieved a neutrophil count greater than 1,000/µL by day 12. There was no episode of thrombocytopenia and no requirement of packed red cell transfusion. As soon as the administration of HDIT and ASCT was finished, the clinical improvement of RA activity was evident. Follow-up clinical assessment was done, six months after treatment. Her RAI decreased to 5. The numbers of tender and swollen joint counts decreased to 3 and 0, respectively. The patient's global assessment of disease status decreased to 20%. The physician's global assessment of disease status was 20%. The patient's assessment of physical function according to the Korean Health Assessment of Questionnaire (KHAQ) was 1.6. Her acute phase reactant values of CRP and ESR were 2.63 mg/dL and 53 mm/hr, respectively. The joint symptom was satisfactorily controlled by the sole use of a nonsteroidal antiinflammatory agent (nabumetone, 1,000 mg/day).

The American College of Rheumatology (ACR) preliminary definition of 50% improvement of RA (ACR50) was fulfilled during the 6 months following ASCT (Fig. 1) (11). Although further long-term follow-up is required, the patient's activity of arthritis has been stable since receiving HDIT with ASCT.

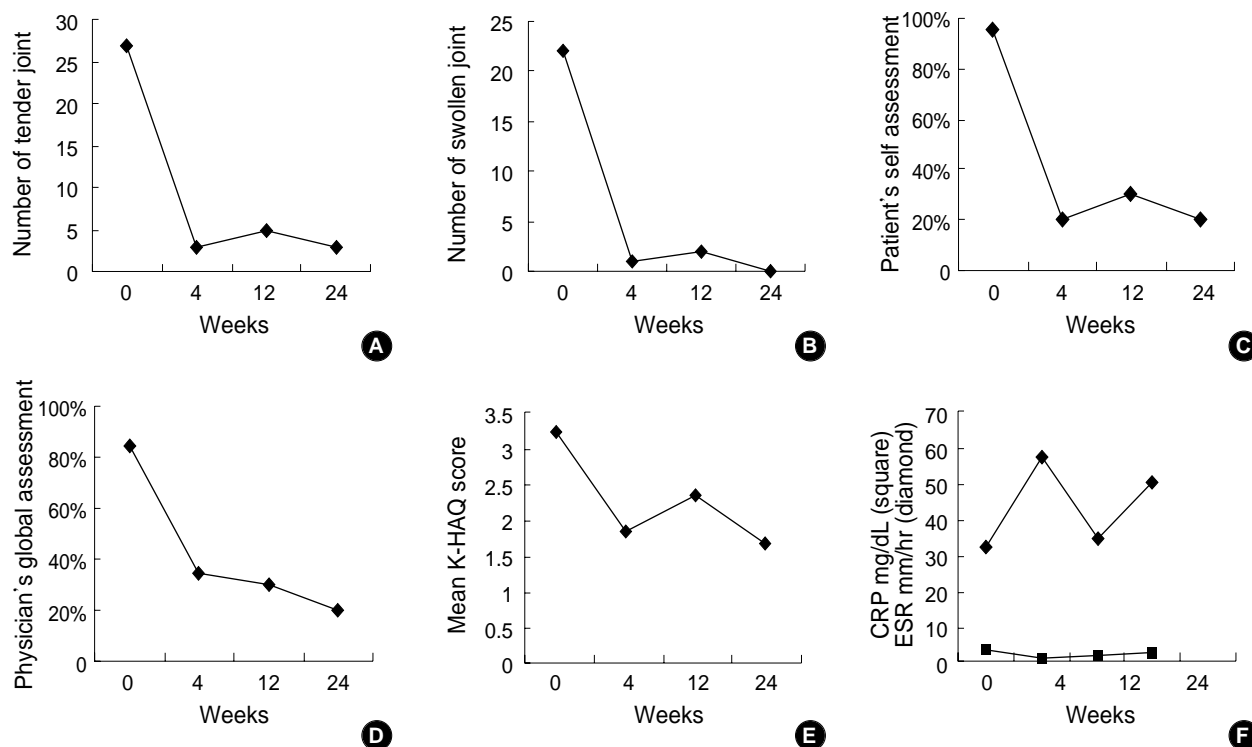


Fig. 1. Clinical courses of the patient after autologous stem cell transplantation. (A) Number of tender joints (of 68 examined), (B) Number of swollen joints (of 66 examined), (C) Patient's self assessment of disease status (0% is best and 100% is worst), (D) Physician's global assessment of disease status (0% is best and 100% is worst), (E) Mean K-HAQ Activities of Daily Living (ADL) score, (F) Erythrocyte sedimentation rate and the C-reactive protein.

DISCUSSION

Over the past five years, an increasing number of patients with autoimmune disease have received HDIT with ASCT. Over 200 transplants have been reported to a registry developed jointly by the European Group for Blood and Marrow Transplantation (EBMT) and the European League Against Rheumatism (EULAR). Approximately 11% of these transplants have been performed for rheumatoid arthritis (RA) (12).

The use of this new treatment has changed from a concept to an undergoing clinical trial. Most reports have emphasized the findings that ASCT can replace disease-causing lymphocytes with normal ones. High-doses of CTX are given to patients to wipe out the "bad" lymphocytes. However, since CTX in high doses has been erroneously believed to destroy the bone marrow's ability to make new blood cells, the method also requires a blood stem cell transplant to prevent this disaster.

Although the population kinetics of synovial cells are not completely understood, many evidences suggest a bone marrow origin for at least that synovial cell subset which is phenotypically similar to macrophages (13). Although it is not clear whether this applies to all synovial cells, other data suggest that there is local proliferation of at least the fibroblast-like synovial cells (14).

The rationale behind HDIT includes; 1) inhibition of the proliferation of synovial cells, 2) induction of apoptosis in synovial cells, 3) decreasing the bone marrow pool of a population of cells destined to become synovial cells (15). Another possible cure for RA could be brought about through the elimination and prevention of the reemergence of the "wrong" macrophages, dendritic cells, and B cells, and through the reverse of the abnormal synovial microenvironment. Although the exact mechanism of HDIT with ASCT on RA treatment has not been fully understood, the rationale is probably to reset the stem cells so that random rearrangements of T-cell and B-cell receptors after autologous transplant would result in a more favorable immunologic repertoire (16).

Despite the difference of CTX doses and the stem cell mobilization protocols, recurrence of disease was noted for all patients, although favorable responses were observed, initially (17, 18). The recurrence rate of RA following HDIT/ASCT is not clear, but the mechanism has been proposed in several reports. They suggest that relapse of RA may be inevitable if chemotherapy-resistant, antigen-presenting cells remain in the synovium, or if circulating T cells that survive HDIT, are infused with the ASCT. Also, the T cells from the redeveloping immune system may arrive at the injured joints and develop into cells that react to arthritogenic peptides remaining in the joint. Therefore, our experience of HDIT/ASCT on refractory RA warrants careful monitoring at least for 12 months after the procedure, even though an initial clinical improvement was achieved.

To prolong the period of complete remission, allogeneic stem cell transplantation may be preferable to autologous since allogeneic cells could conceivably play a role in eradicating abnormal immune cell population (19). Since patients undergoing allogeneic stem cell transplantation are more prone to graft-versus-host disease, infection, bleeding, and are associated with high treatment-related mortality, the procedure is not popular for the treatment of autoimmune disease. However, recently developed approach with non-myeloablative allogeneic stem cell transplantation can substantially reduce treatment-associated toxicity and might be a useful treatment modality (20).

Another limitation of HDIT/ASCT on refractory RA is long-term morbidity and mortality. Some reports have addressed the possible developments of neoplasia, either solid tumors or hematologic malignancies (21, 22). Other complications include infertility, early menopause, and cataracts. Short-term side effects (e.g., mucositis, nausea/vomiting, or neutropenic fever) were more readily controlled compared to long-term morbidity. In transplant data reported to the EBMT-EULAR registry, an 8-9% treatment mortality has been observed for autoimmune disease (2).

Still a number of issues remain to be clarified regarding HDIT/ASCT in the treatment of autoimmune disease. Patient selection is important, and should be done with a reliable identification of what currently available treatment regimens have failed in the patient prior to the entry into these studies. The issue of how to mobilize stem cells may need to be clarified and conditioning regimens also need to be standardized (23). Lastly, the development of appropriate trials is mandatory, which would compare HSCT/ASCT to standard and molecular therapies. Furthermore, multi-center based studies and consensus should be developed for protocol design and end point measurement. After such considerations, HDIT/ASCT will settle down as a more optimal modality in the treatment of RA.

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