INTRODUCTION

It has recently been suggested that high-dose immunosuppressive treatment (HDIT) with autologous stem cell transplantation (ASCT) can be a therapeutic approach for the management of severe autoimmune diseases. 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 × 10⁶ 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

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, Sunnyvale, 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/days 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 HDT, 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 HDT 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 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 (naproxen, 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 HDT 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 H SCT/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.

REFERENCES

1. Snowden JA, Biggs JC, Brooks PM. Autologous blood stem cell transplantation for autoimmune diseases. Lancet 1996; 348: 1112-3.
2. Tyndall A, Gratwohl A. Blood and marrow stem cell transplants in autoimmune 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.
3. Sullivan KM, Furst DE. The evolving role of blood and marrow transplantation for the treatment of autoimmune diseases. J Rheumatol 1997; 48: 1-4.
4. Hahn BH. The potential role of autologous stem cell transplantation in patients with systemic lupus erythematosus. J Rheumatol 1997; 48: 89-93.
5. Clement PJ, Furst DE. Choosing appropriate patients with SSc for
treatment by autologous stem cell transplantation. J Rheumatol 1997; 48: 85-8.

6. Joske DJL, Ma DT, Langlands DR, Owen ET. Autologous bone marrow transplantation for rheumatoid arthritis. Lancet 1997; 350: 337-8.

7. Snowden JA, Biggs JC, Milliken ST, Fuller A, Brooks PM. A phase III dose escalation study of intensive cyclophosphamide and autologous blood stem cell rescue in severe, active rheumatoid arthritis. Arthritis Rheum 1999; 42: 2286-92.

8. Pavletic ZS, O’Dell JR, Bishop MR, Kessinger A, Reed EC, Ursick MM, et al. Treatment of refractory rheumatoid arthritis utilizing an outpatient autologous blood stem cell transplantation protocol. Blood 1998; 92(suppl 1): 370b.

9. Durez P, Toungouz M, Schandene L, Lambermont M, Goldman M. Remission and immune reconstitution after T-cell-depleted stem-cell transplantation for rheumatoid arthritis. Lancet 1998; 352: 881.

10. Bae SC, Cook EF, Kim SY. Psychometric evaluation of a Korean Health Assessment Questionnaire for clinical research. J Rheumatol 1998; 25: 1975-9.

11. Felson DT, Anderson JJ, Boers M, Bombardier C, Burckhardt CS, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995; 38: 727-35.

12. Brooks PM. Stem cell transplantation in auto-immune disease-pleminary lecture APLAR. Proceedings in 9th Asia Pacific League of Associations for Rheumatology Congress p24-8.

13. Edwards JC, Willoughby DA. Demonstration of bone marrow derived cells in synovial lining by means of giant intracellular granules as genetic markers. Ann Rheum Dis 1982; 41: 177-82.

14. Qui Z, Garcia CH, O’Rourke LM, Planck SR, Kohli M, Rosenbaum JT. Local proliferation of fibroblast-like synoviocytes contributes to synovial hyperplasia: Results of proliferating cell nuclear antigen/cyclin, c-myc, and nuclear organizer region staining. Arthritis Rheum 1994; 37: 212-20.

15. Hamilton JA. Rheumatoid arthritis: opposing actions of hematopoietic growth factors and slow-acting anti-rheumatic drugs. Lancet 1993; 342: 536-9.

16. Wicks I, Cooley H, Szer J. Autologous hemopoietic stem cell transplantation: A possible cure for rheumatoid arthritis? Arthritis Rheum 1997; 40: 1005-11.

17. Euler HH, Marmont AM, Bacigalupo A, Fastenrath S, Dreger P, Hoffknecht M, Zander AR, Schalke B, Hahn U, Haas R, Schmitz M. Early recurrence or persistence of immune diseases after unmanipulated autologous stem cell transplantation. Blood 1996; 88: 3621-5.

18. Burt RK, Georganas C, Schroeder J, Traynor A, Stefka J, Schuening F, Graziano F, Mineishi S, Brush M, Fishman M, Welles C, Rosen S, Pope R. Autologous hematopoietic stem cell transplantation in refractory rheumatoid arthritis. Arthritis Rheum 1999; 42: 2281-5.

19. Snowden JA, Kearney P, Kearney A, Cooley HM, Grigg A, Jacobs P, Bergman J, Brooks PM, Biggs JC. Long-term outcome of autoimmune disease following allogeneic bone marrow transplantation. Arthritis Rheum 1998; 41: 453-9.

20. McSweeney PA, Storb R. Mixed chimerism: Preclinical studies and clinical applications. Biol Blood Marrow Transplant 1999; 5: 192-203.

21. Milligan DW, Ruiz de Elvira MC, Kolb JJ, Goldstone AH, Meloni G, Rohatiner AZ, Colombat P, Schmitz N. Secondary leukemia and myelodysplasia after autografting for lymphoma: results from the EBMT. EBMT Lymphoma and Late Effects Working Parties. European Group for Blood and Marrow Transplantation. Br J Haematol 1999; 106: 1020-6.

22. Radis CD, Kahl LE, Baker GL, Wasko MC, Cash JM, Gallatin A, Stolzer BL, Agarwal AK, Medsger TA Jr, Kwoh CK. Effects of cyclophosphamide on the development of malignancy and on long-term survival of patients with rheumatoid arthritis. A 20-yr follow-up study. Arthritis Rheum 1995; 38: 1120-7.

23. Brooks PM. Hematopoietic stem cell transplantation for autoimmune diseases. J Rheumatol 1997; 48: 19-22.