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Hemopoietic stem cell transplantation in refractory rheumatoid arthritis is not a contraindication for reconstructive surgery

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ABSTRACT

Hemopoietic stem cell transplantation (HCST) is an experimental therapy that may produce prolonged remissions in patients with rheumatoid arthritis (RA) resistant to other treatments. Prosthetic articular replacement is often required in severe long-lasting disease. There is a well-founded concern regarding the feasibility and safety of reconstructive surgery after HSCT and as yet no published data on the subject. We report a patient with RA of 9 years' duration resistant to conventional treatments plus femoral head necrosis, who underwent prosthetic hip replacement with no post-surgical complications one year after HSCT, with a sustained reponse.

Case report

Immunoablation followed by autologous hemopoietic stem cell transplantation (HSCT) produces remission in rheumatoid arthritis (RA) refractory to conventional therapy (1, 2). Ideally, a major advantage of the procedure would be expected when performing the transplant before irreversible structural bone and joint damage is established (1), but this is not the case for most of the patients enrolled in the ongoing phase I/II trials. On the other hand, no published experience about reconstructive surgery after HSCT is available to date. We report a resistant to conventional therapy RA patient with a sustained response two years after immunoablation and HSCT, who underwent further surgical replacement of the right femoral head.

Patient and method

Our patient is a 25-year-old woman diagnosed with seronegative RA in 1991 who showed a relapsing and progressive course despite the treatments received (gold salts, methotrexate, hydroxychloroquine, cyclosporine, sulfasalazine, azathioprine, steroids and nonsteroidal antiinflamatory drugs).

Before her stem cell transplant,she was in the ACR 20 response class (American College of Rheumatology Scale) with: 20 swollen and 14 tender joints; 2 hours of morning stiffness; HAQ (Health Assessment Questionnaire) score 2.87; visual analogue scale (VAS) for pain 55 mm; patient's global severity evaluation (VAS) 89 mm; and physician's global severity evaluation (VAS) 83 mm. The laboratory tests revealed ESR 105 mm/h (normal < 10), CRP 110 mg/L (normal < 5), RF 15 UI/mL (normal < 15) and HLA-DR1 (0101)/DR7. She presented with established erosive arthropathy affecting the shoulders, elbows, wrists, hands, right hip, knees and feet, as well as an aseptic necrosis of the right femoral head.

After signed informed consent was obtained, cyclophosphamide (2 g/m^2 x 1 day) and G-CSF (10 mg/Kg/day x 7 days) were administered before performing two cytapheresis; the first one and part of the second were *in vitro* enriched by CD34+ positive selection, and the rest of the second one was kept as a back-up.

As conditioning, she received immunosuppression with cyclophosphamide 50 mg/Kg x 4 days (-6, -5, -4, -3), antilymphocyte globulin 15 mg/Kg/day x 4 days (-5, -4, -3, -2), and methyl-prednisolone 2 mg/Kg/day x 4 days (-5, -4, -3, -2), and presented nausea, vomiting, renal involvement (grade 1), hepatic involvement (grade 1), mucositis (grade 1) and alopecia. She was infused on 2 February 2000 (CD34+ 3.78 and CD3+ 0.027 x 10^6/Kg). The absolute neutrophil count (ANC) nadir (0.0 x10^9/L) was on day +3 and the ANC recovery (> 0.5 x10^9/L) was on day +12. During aplasia the patient suffered self-limited gynecological hemorrhage and an acute bacterial pulmonary infection which resolved with specific antibiotherapy, was transfused with 8 red cell concentrates and 11 single donor platelet units, and required 3 days of parental nutrition. She was discharged on day +21 and has been evaluated every three months.

The one-year post-transplant evaluation showed an ACR 70 response: 2 swollen joints, 3 tender joints, HAQ 2.3, pain 25 mm, patient's global severity 40, physician's global severity 45, and morning stiffness 15 minutes. Her most severe problem was aseptic necrosis of the right femoral head, which was surgically replaced 12 months after the autotransplant with no sequelae to surgery. At the time of the operation the

patient's peripheral blood counts were normal, and regarding her immune reconstitution status, she had recovered the T subsets (T lymphocytes: 793/uL; T4: 312/uL; T8: 286/uL; and suppressor T cells had also increased: NK: 416/L), although B-cell counts remained slightly low (B lymphocytes: 65/uL). The two-year post-transplant evaluation showed neither swollen joints nor morning stiffness, and only one tender joint persisted. At present her only treatment is once or twice-daily analgesics, and laboratory tests remain in normal ranges. In addition, she is on specific rehabilitation treatment, and nowadays can walk without help, and has resumed her university studies.

Discussion

The analysis of the existing data has recently confirmed that high-dose immunosuppression and autologous HSCT are relatively well tolerated, achieving significant responses in most patients, with frequent ACR 50-70, although disease reactivation is to be expected (1). In addition, a renewed sensitivity of RA to disease modifying antirheumatic drugs (DMARD), suggesting a "re-setting" of the immune system after the procedure, has been confirmed.

Further prosthetic surgical replacement is frequently required in RA patients (1), and some concern has been raised regarding the performance of such a procedure after high dose immunosuppression and autologous rescue. This is due to a possibly increased susceptibility towards prosthesis-related infection, caused by altered post-transplant immune reconstitution. On the other hand, prosthetic surgical replacement may be a valuable tool for improving both functional capacity and quality of life in RA patients after HSCT. Our patient is in remission two years after the transplant. She underwent early orthopedic surgical replacement of the right femoral hip, with an uncomplicated post-surgical evolution, thus showing that HSCT is not a contraindication for reconstructive surgery.

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