High dose chemotherapy and syngeneic stem cell transplantation in a patient with refractory rheumatoid arthritis: poor response associated with persistence of host autoantibodies and synovial abnormalities

M van Oosterhout, R J Verburg, E W N Levarht, J D Moolenburgh, R M Barge, W E Fibbe, J M van Laar

Background: Immunoablative therapy combined with haematopoietic stem cell transplantation (SCT) is a possible treatment for patients with severe rheumatoid arthritis (RA). Case report: A patient with rheumatoid factor positive, progressively erosive RA, refractory to treatment, was treated with high dose cyclophosphamide, followed by reinfusion of an unmanipulated peripheral blood graft derived from her identical twin sister. The clinical response was unsatisfactory, necessitating reinstitution of treatment with disease modifying antirheumatic drugs, which was associated with persistence of host serum autoantibodies and a cellular infiltrate in synovium, notably of plasma cells. Discussion: The effectiveness of syngeneic SCT may be critically dependent on the degree of immunoablation achieved or on the composition of the graft.

RESULTS

Before conditioning, DMARD treatment was discontinued, which resulted in a disease flare (fig 1). The conditioning regimen was well tolerated by the patient. She was discharged on day 14 without joint complaints. The nadir of neutrophils was on day 8 (0.016×10⁹/l). After 1 month disease activity flared accompanied by an acute phase response. Intra-articular injection with 80 mg of methylprednisolone into the left knee was ineffective and 2 months after transplantation arthroscopic lavage of the knee including synovial biopsies was performed followed by a repeat arthroscopy 1 month later. Both synovial fluid and tissue were cultured for micro-organisms at both occasions, but the results were negative. Prednisone was maintained at a dose of 7.5 mg/day and methotrexate was reinitiated at incremental doses 15 weeks after the transplantation because of persistent disease activity. The patient was then readmitted because of disabling pain of her left knee caused by progressive osteoarthritis, leading to joint replacement surgery at 6 months after the transplantation. Joint radiographs 1 year after transplantation showed progression of joint erosion in hands, feet, ankles, and left elbow as well as loss of cartilage thickness in hand and feet joints and the right knee.

In the 2 years after the transplantation the patient again underwent orthopaedic operations. RF and antibodies against CCP and parvovirus B19 remained detectable during follow up. After failure of adding leflunomide, parenteral gold, and anakinra respectively to methotrexate, adalimumab was started alongside methotrexate, with a moderate response. Figure 1 shows the course of the clinical and laboratory measures.

Abbreviations: CCP, cyclic citrullinated peptide; DMARDs, disease modifying antirheumatic drugs; G-CSF, granulocyte colony stimulating factor; IV, intravenously; RA, rheumatoid arthritis; RF, rheumatoid factor; SCT, stem cell transplantation
Autologous SCT in patients with RA have been proposed. Causes for failure to achieve permanent remission with sensitivity to DMARD treatment seemed restored. Several factors may have contributed to this outcome. Firstly, our patient was seropositive and after treatment RF, anti-CCP, and anti-parvovirus B19 remained positive, suggesting that the host plasma cells were not eradicated by the high dose chemotherapy nor replaced by new donor derived plasma cells from the graft, which contained <1% CD19+ cells. This notion was supported by the persistence of plasma cell infiltration in the synovial tissue after transplantation. Secondly, because of safety concerns in a heavily pretreated patient, we opted not to use antithymocyte globulin in the conditioning regimen. Conceivably, this may have resulted in insufficient reduction of autoreactive lymphocytes. Thirdly, although the graft was enriched for mononuclear cells, granulocytes constituted a significant proportion of the graft. These cells may have been activated as a result of mobilisation with G-CSF, enabling them to home to the synovium and act as effector cells.

Because of the syngeneic setting of the transplantation, we were unable to detect chimerism after transplantation, but the rapid rise in CD45RA+ CD4+ lymphocytes in the circulation within 2 weeks probably reflects a population of donor derived CD19+ cells. This notion was supported by the persistence of plasma cell infiltration in the synovial tissue after transplantation. These cells may have been activated as a result of mobilisation with G-CSF, enabling them to home to the synovium and act as effector cells.

In conclusion, our patient was treated with high dose chemotherapy and syngeneic SCT but her disease flared after 1 month. The persistence of serum autoantibodies and marked neutrophilic and plasma cell infiltration of the synovium may have contributed to the rapid flare of RA. Preliminary data suggest transplantation of an allogeneic graft may be more effective in eradicating host immune cells than an autologous or syngeneic graft by induction of a graft-versus-autoimmunity effect. Improved and less toxic conditioning schemes make SCTs, even allogeneic transplantsations, applicable in an increasing group of patients with rheumatic diseases refractory to conventional antirheumatic drugs and biological agents.

**ACKNOWLEDGEMENTS**

Dr I Bajema, Department of Pathology, for providing the haematoxylin and eosin colour figures.

**Authors’ affiliations**

M van Oosterhout, R J Verburg, E W N Levarht, J M van Laar, Department of Rheumatology, Leiden University Medical Centre, The Netherlands

J D Moolenburgh, Department of Rheumatology, Medical Centre Alkmaar, The Netherlands

R M Barge, W E Fibbe, Department of Haematology, Leiden University Medical Centre, The Netherlands

1784 van Oosterhout, Verburg, Levarht, et al

www.annrheumdis.com
Correspondence to: Dr J M van Laar, Department of Rheumatology, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands; J.M.van_Laar@LUMC.nl

Accepted 14 April 2005

REFERENCES

Figure 2. Haematoxylin and eosin staining (A–D) at baseline (A and B) and after 2 months (C and D) showing marked infiltration of plasma cells and neutrophils. Peroxidase staining (E–H) after 2 months for CD5 (E), CD38 (F), CD3 (G), and CD138 (H). Original magnification ×100 (A and C, E–H) and ×400 (B and D).