CONCISE REPORT

# Autologous haematopoietic stem cell transplantation for Behçet's disease with pulmonary involvement: analysis after 5 years of follow up

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**Background:** Myeloablative chemotherapy and autologous haematopoietic stem cell transplantation (HSCT) may provide a therapeutic option in severe Behçet's disease (BD) with pulmonary involvement.

**Case reports:** Two patients with BD with pulmonary involvement refractory to conventional immunosuppressive treatment underwent HSCT 1999. Stem cells were mobilised with cyclophosphamide (2 and 4 g/m$^2$) and subsequently enriched ex vivo for CD34+ cells. The conditioning regimen used was melphalan (200 mg/m$^2$). Outcome was measured by improvement of clinical features, function of affected organs, serological markers, need for immunosuppressive chemotherapy after transplant, and relapse. In both cases HSCT was successful, with good response and without serious complications. After 5 years of follow up one patient is in complete remission without immunosuppressive drugs and one has partial remission, needing low dose corticosteroids (8 mg/day).

**Conclusion:** In these two patients myeloablative chemotherapy, followed by HSCT could be performed safely with marked improvement. In comparison with other observational studies the duration of more than 5 years of remission is remarkable, and its full duration is still unknown.

Behçet's disease (BD) is an inflammatory disorder with supposed genetic susceptibility, characterised by recurrent orogenital ulcers, skin lesions, and uveitis. Involvement of other organs is less common, but often life threatening.[1] Although its aetiology is still unknown, remarkable research has been carried out into the causation and pathophysiology underlining the role of molecular and immunological mechanisms, especially of T cell mediated immunity with production of tumour necrosis factor α (TNFα) and other proinflammatory cytokines.[2] Pulmonary arterial involvement as a rare, but severe complication of BD is often refractory to conventional immunosuppressive chemotherapy.[3] Despite a significantly better outcome with early recognition and treatment,[4] HSCT sometimes provides the last option of successful treatment, for which the rationale is based on the hypothesis of a reconstitution of the immune system[5] or of a shift towards self tolerance.[6]

Our two patients underwent haematopoietic stem cell transplantation (HSCT) 1999 after 48 and 15 months of disease activity.[7] We now report the 5 year, almost 6 year, outcome of these two patients.

## CASE REPORTS

Diagnosis was made on the basis of the criteria proposed by the International Study Group for BD in 1990.

The first patient was a 32 year old German man, presenting with fever, recurrent aphthous ulcers, erythema nodosum, polyarthritis, and an intracardiac thrombus. His disease was controlled with high doses of corticosteroids. Later on, haemoptysis and pulmonary artery aneurysms in the right lung developed, resistant to cyclophosphamide and methotrexate (oral application) and requiring high doses of corticosteroids.

The second patient, a 49 year old Turkish man, had fever, recurrent aphthous ulcers, Coombs' negative haemolytic anaemia, posterior uveitis, and involvement of the lung (pulmonary artery aneurysms) and central nervous system (subcortical and periventricular vasculitic lesions). Partial remission was achieved while he was being treated with oral cyclophosphamide and prednisone, but relapse occurred when the dose was reduced.

The study protocol comprised two cycles of mobilisation treatment with cyclophosphamide (2 g/m$^2$ and 4 g/m$^2$) and subcutaneous administration of granulocyte-colony stimulating factor (G-CSF; 10 μg/kg body weight (BW)), followed by stem cell harvest and CD34 selection. Melphalan (200 mg/m$^2$) was chosen as the conditioning regimen because of its low toxicity, its myeloablative effect, because of long therapeutic experience, and because of its safe application in patients with renal failure.

Both patients were asked to return to our outpatient department 2 and 6 months after transplantation, depending on their state of health. Examination included physical examination, measures of laboratory features, pulmonary function testing with carbon monoxide transfer factor, echocardiogram, computer tomography of the chest, and magnetic resonance imaging of the brain (for the second patient).

In both cases HSCT after myeloablative chemotherapy has been successful, including improvement in the clinical and radiological findings of chest and brain. Both patients achieved immunological reconstitution within 2 years as judged by CD4/CD8 and CD45 RA+.

The first patient had complete remission of all his previous disease manifestations and did not need any immunosuppressive drugs in 5 years of follow up.

In the second patient HSCT led to a partial remission with complete resolution of pulmonary affection. Because of recurrent orogenital ulcers he was given a low dose corticosteroid treatment, which had to be slowly augmented from 2.5 mg/day 10 months after transplantation, up to 5 mg/day in September 2000 and 8 mg/day since December 2003. Until June 2004 (last visit) the course of his disease was stable.

**Abbreviations:** BD, Behçet's disease; G-CSF, granulocyte-colony stimulating factor; HSCT, haematopoietic stem cell transplantation; TNFα, tumour necrosis factor α

**Table 1** Pre- and post-transplant course of disease and immunosuppressive treatment

| Age at HSCT (years) | Sex/ nationality | Major symptoms at point of primary diagnosis | Developing complications | Pretransplant immunosuppressive treatments | Reason for HSCT | Duration of disease until HSCT (months) | Stem cell mobilisation with: | Leukapheresis | Enrichment ex vivo with CD34+ cells | Conditioning regimen | HSCT | Course after HSCT | Response and outcome | Current immunosuppressive drugs |
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| 32 | Male/ German | Fever, recurrent aphthous ulcers, polyarthritis, erythema nodosum, intracardiac thrombus | Haemoptysis, pulmonary artery aneurysms | High dose corticosteroids (up to 100 mg/day) for 48 months, methotrexate (40 mg/week IV) for 5 months, cyclophosphamide 150 mg/day and corticosteroids 250 mg/day for 5 months | High disease activity with life threatening organ involvement (pulmonary bleeding) refractory to conventional chemotherapy | 48 | Two cycles of cyclophosphamide (2 g/m$^2$ and 4 g/m$^2$), G-CSF (10 µg/kg BW) | Twice: $2.9\times10^9$/kg BW, no selection possible; $7.1\times10^6$/kg BW, after selection $5.1\times10^6$/kg BW | Yes | Melphalan (200 mg/kg BW) | March 1999 | Time to achieve leucocytes >1000: remission 9 days; fever: 1 day; antibiotics for 2 days; 4 platelet transfusions | Complete remission | None |
| 49 | Male/ Turkish | Fever, aphthous ulcers, posterior uveitis, Coombs' test negative haemolytic anaemia, central nervous system involvement | Oral cyclophosphamide and corticosteroids (Fauci scheme) for 10 months | | | 15 | | Twice: $4.3\times10^9$/kg BW, no selection possible; $7.8\times10^6$/kg BW, after selection $3.6\times10^6$/kg BW | | | Nov 1999 | Time to achieve leucocytes >1000: response 6 days; fever: 1 day; antibiotics for 7 days; 3 platelet transfusions | Partial response (recurrent oral and genital aphthous ulcers) | Corticosteroids (8 mg/day) |

Table 1 shows the course of disease before and after treatment and the treatment given

## DISCUSSION

BD is a multisystemic vasculitis of unknown origin. Immunological dysregulation, possibly due to modulating effects of gene polymorphisms, seems evident, with a key role of γδ T cells in pathogenesis and progression.[2] Up regulated cytokine production of interferon γ, interleukin 12, interleukin 8, and TNFα with subsequent induction of adhesion molecules permitting accumulation of autoreactive T cells at inflammatory sites is another step in the development of inflammatory processes.[8] These and other genetic and molecular discoveries not only provide a rationale for new forms of immunomodulation in the treatment of BD but also may contribute to early identification of patients at high risk and thus enable appropriate individual treatment.

Therapeutic approaches evolved empirically because the causative and pathogenic mechanisms were unknown. Current treatment includes—depending on disease activity and severity—immunosuppression with, for example, corticosteroids, colchicine, sulfasalazine, azathioprine, methotrexate, ciclosporin, cyclophosphamide, or immunomodulation with thalidomide, and anticoagulation.[1] Increasing knowledge of molecular mechanisms and failure of conventional chemotherapy in cases of fatal organ involvement are the basis of new therapeutic strategies. These include the development of monoclonal antibodies like TNFα inhibitors[9 10] or cytokines like interferon α[11] or performance of autologous HSCT not only in haematological and/or oncological disease but also in severe autoimmune diseases.[12] Their common aim is the depletion or inhibition of autoreactive T cells. Myeloablative treatment followed by HSCT may exert two possible effects: autoreactive T cell clones may be destroyed by cytotoxic treatment with subsequent repopulation of bone marrow and peripheral blood by ''healthy'' stem cells.[5] Another explanation is the persistence of autoreactive cells in a reduced number, which are ''overwhelmed'' by the autologous graft's induction of tolerance.[6]

Immunosuppressive drugs have a remarkable risk of (opportunistic) infections and yet unknown duration of treatment. In comparison, HSCT with increasing safety provides a real alternative to patients with BD who have a fatal course of the disease. TNFα inhibitors, on the other hand, despite promising short term effects[9] with reduction of disease activity[9] fail to induce stable remission in patients with life threatening organ involvement who need continuing immunosuppression.[13]

In our two patients HSCT has been beneficial, with good response and outcome and a stable course for 5 years of follow up after transplant. A report of Traynor *et al*—an analysis of the outcome of 15 patients with severe systemic lupus erythematosus with a median follow up after transplant of 36 months—showed similar encouraging results, with remarkable improvement and sustained withdrawal of immunosuppressive treatment in most patients.[14] Similarly, Rossi *et al* recently reported the successful treatment of a 4 year old girl with refractory intestinal BD who had complete drugs-free remission 2 years after HSCT.[15] Despite these hopeful reports toxicity is still a worry according to a meeting report on ''HSCT in the treatment of severe autoimmune diseases 2003''[12] and a retrospective registry survey on HSCT for systemic lupus erythematosus, carried out by the European Blood and Marrow Transplant and the European League against Rheumatism (EBMT/EULAR) registry.[16] These data demonstrated not only the efficacy but also the high morbidity and overall mortality (up to 9%) of HSCT, with significant variation between the conditioning regimen given and the diseases treated.

## CONCLUSION

HSCT seems to provide a real therapeutic option for patients with severe or refractory BD. It is safe and effective when performed in centres with experience in transplantation and the clinical course of this autoimmune disorder. Most patients so far experience complete or partial remission, with improved organ function and no immunosuppressive treatment or a reduced need for it. Further research on molecular mechanisms of the pathogenesis of BD and stem cell differentiation will be the basis for new therapeutic strategies. The role of HSCT in comparison with recent therapeutic approaches like TNFα inhibitors, monoclonal antibodies, or interferon α in patients with severe or refractory BD has to be determined in future studies.

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