A successful case of second autologous haematopoietic stem cell transplantation for post-transplant systemic sclerosis relapse

Sirs,

It has been reported that autologous haemopoietic stem-cell transplantation (aHSCT) is a very effective therapeutic option for patients with severe systemic sclerosis (SSc) (1). We report a successful case of second aHSCT for post-transplant systemic sclerosis relapse.

In June 2007, the 24-year-old female noted the development of characteristic Raynaud phenomenon, associated with puffy fingers and reflux oesophagitis. Skin thickening progressed proximally in the hands and feet. Laboratory test showed positive anti-Scl-70 antibody and antinuclear antibody. She was diagnosed as systemic sclerosis and treated with a initial dose of 30 mg/day prednisone before tapering to a dose of 10 mg/day. In 2008, her skin lesions had progressed to the truck with limited motion of mouth, wrist, knees, and elbows. Therefore, oral cyclophosphamide (100 mg/day) was added in combination with conventional prednisone. However, the skin lesions continued to deteriorate even after 6 months of treatment (cyclophosphamide cumulative dose of 17 gr). In March 2011, her modified Rodnan skin score (mRSS) was 38, and pulmonary function tests showed that her diffusing capacity of carbon monoxide was 52%, predicted FVC 58%. As a refractory diffuse SSc to conventional treatment with rapid progression of skin and lung involvement within the 4 years from the onset, we considered the patient an eligible candidate for aHSCT. The patient had a weight of 37.5 kg and a height of 161 cm. The transplant regimen consisted of mobilisation with i.v. cyclophosphamide (2g) and G-CSF followed by leukapheresis and CD34 selection of the autologous graft. Conditioning was performed with i.v. cyclophosphamide (2g/day for 4 days) followed by $cd34^+$ $2.21x10^6$/kg graft. After transplantation, she only had 5 mg/day prednisone. 3 months later, her mRSS decreased to 22 and she had significant remission of skin fibrosis, which was associated with recovery of joint motion and improvement in her quality of life. Unfortunately, in December 2011, she had disease relapse with worsened skin lesions and impaired movement of elbow and knee joint. The mRSS increased up to 31. Moreover, ground-glass opacity was seen on chest high-resolution CT. On pulmonary function test, her diffusing capacity of carbon monoxide was 47%, predicted FVC was 43%. Thus a second aHSCT was carried out in February 2012. (mobilisation with i.v. cyclophosphamide 3g and G-CSF; Conditioning with i.v. cyclophosphamide 3g for 2 days, 2g for 1 day, rabbit antithymocyte globulin 100 mg for 3 days; followed by $cd34^+$ $1.5x10^6$/kg graft). In June 2012 her mRSS reduced to 23. Then a preventive regimen of methotrexate (10 mg/week) and prednisone 10 mg/day were used. In December, her mRSS was 18 and her weight increased by 2 kg. In April 2013, her mRSS was 13. Until the last outpatient visit in November 2014, the patient was still in remission state, her mRSS was 9, and her respiratory function remained stable.

To our knowledge, this was the first successful case of repeat administration of aHSCT in SSc patients who had a disease relapse after the first transplant. The patient had been treated with cyclophosphamide and prednisone, but her skin lesions continued to deteriorate. Therefore, we treated her with aHSCT. She responsed very well with decreased mRSS and increased joint motion. But 9 months later, the disease relapsed with pulmonary fibrosis. Due to her good response to the first transplantation, we carried out a second aHSCT. As we expected, she showed an excellent response to the treatment.

SSc remains a difficult-to-treat disease despite the current conventional therapy. As an intensive immunomodulatory therapy, aHSCT has been suggested for severe treatment-resistant autoimmune diseases. To date, three controlled trials have been done, The American Scleroderma Stem Cell *versus* Immune Suppression Trial (ASSIST) (2), The Autologous Stem cell Transplantation International Scleroderma trial (ASTIS) (3) and The Scleroderma: Cyclophosphamide Or Transplantation (SCOT) trial. The available data indicate that aHSCT may result in significant and sustained clinical benefits for carefully selected patients, while, on the other hand, a higher morbidity rate compared with standard treatments. In ASTIS study, the reported treatment-related mortality was 10.4% (3). Rheumatic disease patients seem to be even more at risk to develop secondary autoimmune diseases after they had aHSCT (4, 5). Long-term follow-up of transplanted SSc patients is essential.

Disease relapse after aHSCT is a challenge for rheumatologists. In the ASTIS trial, 22.4% patients in the aHSCT group had disease relapse between 12 and 24 months (2). However, no widely-approved guideline or agreement for post-transplant patient is available till now. An on-going United States of America multicentre HSCT trial for systemic sclerosis, referred to as the STAT trial (Scleroderma Treatment with Autologous Transplant) (NCT01413100), has been conducted to find out whether 2 years of post-HSCT mycophenolate mofetil maintenance therapy is able to prevent or delay the recurrence of SSc after aHSCT (6).

Repeat aHSCT has been used in neoplastic patients. Some research confirmed that a second aHSCT can be applied to patients who had a good response to the first. For example, haematologists have agreed that repeat administration of high-dose melphalan with autologous transplantation in multiple myeloma patients who relapse following a first transplant could be considered (7). In our case, we had been facing a similar situation though diffuse SSc was a non-neoplastic disease. aHSCT treatment in early diffuse SSc fundamentally alters the long-term outcome of patients with poor-prognosis SSc (4). When the disease relapse, the long-term outcomes are poor. And our experience indicated that some SSc patients could benefit from the second aHSCT, who had relapsed disease after the first successful aHSCT. However, the high treatment-related mortality should be always taken into account before carrying out a second aHSCT for SSc patients. And further trial was needed to find out the appropriate indications of its clinical application.

Y. HOU[1], *MD*, *PhD*
H.-J. LI[2], *MD*
M.-T. LI[1], *MD*, *PhD*
D. XU[1], *MD*, *PhD*
D.-B. ZHOU[3], *MD*
X.-F. ZENG[1], *MD*

[1]Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital; [2]Department of Haematology, Handan First Hospital, Hebei, China; [3]Department of Haematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China.

Address correspondence to:
Prof. Xiao-feng Zeng, Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 100730 Beijing, China.
E-mail: xiaofeng.zeng@cstar.org.cn

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