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Hematopoietic stem cell transplantation for autoimmune diseases in developing countries: current status and future prospectives

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Summary:

In this paper we present preliminary results of hematopoietic stem cell transplantation for autoimmune diseases in Brazil and China. Chinese experience transplanting lupus is significant and the Brazilian experience with several autoimmune diseases is growing. We discuss peculiar conditions in developing countries which could affect the results, and future prospectives for the organization of phase III randomized trials in those countries.
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Application of hematopoietic stem cell transplantation (HSCT) for the treatment of systemic autoimmune diseases (AID) in developing countries requires consideration of peculiar aspects of the diseases and of the health system in those countries, including: (1) Probably a worse activity and prognosis of severe AID in the patient population treated with conventional therapy due in part to poor economical and social conditions.[1] (2) High prevalence of some autoimmune diseases such as rheumatic fever and some forms of pemphigus in Brazil and of systemic lupus erythematosus (SLE) in China (70/100 000). (3) Difficult access to new technologies (stem cell selection columns, monoclonal antibodies, etc) and therapies (anti-TNF agents, new immunosuppressive drugs), which impairs the capacity to deliver the best medical treatment to the patients and to participate in international cooperative trials. (4) Universal coverage of health care by the state, but in a highly regulated fashion for high-cost therapies such as HSCT. (5) Large availability of HLA-identical donors (>50%) in the general population in some countries, like Brazil[2] but not in others, like China. In this work we present preliminary results of HSCT for AID in two big developing countries, Brazil and China, and discuss characteristics and prospectives of the programs, which could apply to other developing countries.

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HSCT for AID in Brazil

Bone marrow transplantation centers in Brazil have a large experience transplanting hematologic autoimmune diseases, such as acquired aplastic anemia, including the design of new conditioning regimens for hypertransfused/presensitized patients,[3] and anecdotical cases of systemic autoimmune diseases submitted to autologous HSCT have been reported since 1996 with favorable results.[4]

In October 2000, a meeting was organized in Ribeirão Preto, Brazil, to launch a program of HSCT for autoimmune diseases in the country. International experts from USA (Richard Burt, Dhaval Patel, William Burns) and Europe (Renate Arnold) met with representatives of main BMT/Rheumatology/Neurology Brazilian groups and it was decided to start a pilot, phase I/II national cooperative study of autologous transplantation for refractory systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and multiple sclerosis (MS). Mobilization of HSC is performed with cyclophosphamide (2 g/m^2) plus G-CSF (10 μg/kg/day) and conditioning is CY + ATG for SLE, BEAM + ATG for MS and CY + Fludarabine + ATG for SSc. Horse ATG is given at 15 mg/kg (three doses before stem cell infusion and three doses after infusion) to replace *in vitro* T-cell depletion/SC selection.[5] Conditioning for SLE and MS followed standard protocols used elewhere,[6,7] while for SSc a highly immunosuppressive combination was adapted from mini-allo transplants.[8] The program started in June 2001 and eight transplants have been performed under the protocol (four for SLE, three for MS and one for an overlapping syndrome of SLE + SSc) in three centers, and other centers are obtaining IRB approval and accruing patients to be engaged in the protocol. Preliminary results show beneficial effects in most patients (three SLE and two MS patients) and an initial significant morbidity/mortality of the transplant procedure because of specific problems of the patient group (kidney failure and fluid overload in three

lupus nephritis, disease flare in one SSc + SLE and high toxicity in one advanced MS). These problems certainly will be overcome with a better patient selection and acquisition of more experience by the centers in managing special transplant-related complications in autoimmune patients.

The main obstacles for the development of the program are the competition for beds in the existing BMT Units and the difficult interaction between transplant and autoimmune specialties for patient accrual. On the other hand, there is great interest and pressure of the patient population to speed the transplant program. Future plans are continuation of phase I/II protocols for MS, SSc and SLE, expansion of these protocols to other immune-mediated diseases (rheumatoid arthritis, pemphigus, inflammatory bowel diseases, diabetes, idiopathic pulmonary fibrosis, etc) and then engage in phase III randomized studies. Possibilities of randomization that are under consideration are: (1) positive selection of CD34 stem cells *vs* unmanipulated transplants, (2) ATG *vs* CAMPATH for *in vivo* T-cell depletion, (3) TBI or busulfan-based conditioning regimens *vs* standard regimens, (4) transplantation *vs* best conventional treatment,[9] as done in developed countries, (5) autologous *vs* mini-allo transplants. This latter randomization could be done on a biological basis, between patients with and without an HLA identical donor, because of the large size of Brazilian families.[2]

HSCT for AID in China

The first patient with an autoimmune disease transplanted with hematopoietic stem cells in China was a lupus patient treated in 1998 at the Affiliated Drum Tower Hospital of the Nanjing University Medical College. After a visit by Dr Richard Burt at Nanjing in 1999, three other centers launched their programs of HSCT for AID: the Union Hospital in Beijing, the Third People's Hospital in Zhengzhou and the Taian People's Hospital in Shandong.

The initial experience of the Nanjing University was reported in 1999 at the Worcester Translational Research Conference and subsequently in Chinese.[10] Autologous bone marrow was collected from three SLE patients, cryopreserved at 4°C and infused after 56 h and conditioning with Cytoxan (CY) 120 mg/kg and Melphalan (140 mg/m^2). G-CSF was given after transplantation and the three patients achieved clinical and laboratorial remission. Subsequently, conditioning regimen was changed to CY (200 mg/kg) plus ATG (90 mg/kg) for SLE and BEAM + ATG for MS, and CD34$^+$ selected and cryopreserved PBSC were used as the source of SC. The group at the Nanjing University performed HSCT for 18 patients with AID (seven SLE and 11 MS). Most patients improved after transplantation (5/7 SLE and 7/11 MS), one patient with SLE and three with MS showed stabilization of the disease, one MS patient progressed and another with lupus died of uncontrolled pulmonary hypertension and congestive heart failure 6 months post-transplantation. The Nanjing group intends to expand its series of autologous HSCT for SLE and MS, and target other inflammatory diseases such as rheumatoid arthritis, SSc, inflammatory bowel disease and myasthenia gravis. There are also plans of participation in phase III trials active in developed countries.

During the EBMT meeting in 2002, the Zhengzhou group reported its experience in autologous HSCT transplantation of 18 patients with SLE.[11] Six patients received BM (median of 1.1×10^8 nucleated cells/kg) and 12 patients received PBSC (3.01×10^6 CD34 + cells/kg), neither product was manipulated *in vitro*. Mobilization was accomplished with CY (2 g/m^2) plus G-CSF (250 μg/day) and the conditioning regimen combined total lymphoid irradiation (8–12 Gy), CY (50 mg/kg/day $\times$ 3) and rabbit ATG (Fresenius, 10 mg/kg/day at days +1 and +2) for *in vivo* T-cell depletion. Haematopoietic engraftment was achieved in 100% of patients with a median time of 15 days (12–18), B lymphocytes were markedly reduced and NK cells were increased 8–12 months post-transplantation. Two-thirds of the patients (12/18) had complete remission, three patients had a partial response and three patients did not respond after a median follow-up of 12 months (3–26 months), and there were no transplant-related deaths.

The Beijing group performed CD34-selected autologous HSCT in 11 patients (eight SLE, one RA, one SSc, one SjS). Conditioning was Cy + ATG ($N = 7$) or Cy + TBI ($N = 4$). All patients achieved clinical remission and three patients developed CMV infection. The Shandong group apparently did only one HSCT for SLE and the patient relapsed after transplantation.

Conclusions

Developing countries are able to produce significant results using HSCT for AID. In fact, the Chinese experience with lupus is already impressive regarding the numbers and outcome and the Brazilian experience is growing. Engagement in phase III randomized trials needs careful selection to answer specific questions relevant for our conditions such as the role of expensive *in vitro* manipulation of stem cells and the comparison of HSCT with expensive medical treatments such as anti-TNF agents for rheumatoid arthritis. Development of those trials depends on the results of present pilot studies, encouraging referral of early-stage patients, and availability of resources. Alternatively, we may join phase III clinical trials active in developed countries, but we may need their help for some resources. Finally, in our countries, one-shot therapy like HSCT is usually cheaper and have a more favorable cost–benefit ratio than prolonged immunosuppression needed for a subgroup of severely affected AID patients. Thus, we can benefit a large number of patients and give a significant contribution to the field, like that shown by Fassas *et al*[12] in Greece transplanting MS. Our experience certainly will encourage other developing countries to overcome various obstacles and implement programs of HSCT for AID.

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References

1 Johnson AE, Cavalcanti FS, Gordon C *et al*. Cross-sectional analysis of differences between patients with systemic lupus erythematosus in England, Brazil and Sweden. *Lupus* 1994; **3**: 501–506.
2 Voltarelli JC, Stracieri ABPL. Aspectos imunológicos dos transplantes de células tronco hematopoéticas (Immunological aspects of haematopoietic stem cell transplantation). *Medicina (Ribeirão Preto)*, 2000; **33**: 443–462.
3 Medeiros CR, Bitencourt MA, Zanis-Neto J, Pasquini R. Busulfan and cyclophosphamide (Bu + Cy) as conditioning regimen to transfused patients (pts) younger than 20 years old treated with bone marrow transplantation. *Blood* 1998; **92**: 135a.
4 Ferreira E, Ribeiro A, Bacal NS *et al*. Transplante de células tronco periféricas autólogas no tratamento de doença autoimune: Remissão completa da anemia hemolítica por aglutininas a frio e concomitante vasculite (Autologous peripheral blood haematopoietic stem cell transplantation in the treatment of an autoimmune disease: complete remission of cold agglutinin hemolytic anaemia and concomitant vasculitis). *Bol Soc Bras Hematol Hematol* 1996; **18** (Suppl): 191.
5 Voltarelli JC. Haematopoietic stem cell transplantation for autoimmune diseases in Brazil. Comment status and future prospectives. *Rev Bras Hematol Hemoter* 2002; **24**: 206–211.
6 Traynor AE, Schroeder J, Rosa RM *et al*. Treatment of severe systemic lupus erythematosus with high-dose therapy and hematopoietic stem cell transplantation: a phase I study. *Lancet* 2000; **356**: 701–707.
7 Comi G, Kappos L, Clanet M *et al*. Guidelines for autologous and marrow stem cell transplantation in multiple sclerosis: a consensus report written on behalf of the European Group for Blood and Marrow Transplantation and the European Charcot Foundation. *J Neurol* 2000; **247**: 376–382.
8 Anderlini P, Giralt S, Andersson B *et al*. Allogeneic stem cell transplantation with fludarabine-based, less intensive conditioning regimens as adoptive immunotherapy in advanced Hodgkin's disease. *Bone Marrow Transplant* 2000; **26**: 615–620.
9 White B, Moore WC, Wigley FM *et al*. Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. *Ann Intern Med* 2000; **132**: 947–954.
10 Ouyang J, Sun LY, Yang YG *et al*. A pilot study in treatment of systemic lupus erythematosus by autologous bone marrow transplant. *Chin J Intern Med* 2001; **40**: 229–231.
11 Zhao J, Fu Y, Peng X. Autologous hematopoietic stem cell transplantation in the treatment of systemic lupus erythematosus. *Bone Marrow Transplant* 2002; **29** (Suppl 2): S15.
12 Fassas A, Anagnostopoulos A, Kazis A *et al*. Autologous stem cell transplantation in progressive multiple sclerosis – an interim analysis of efficacy. *J Clin Immunol* 2000; **20**: 24–30.