Bone Marrow Transplantation (2008) 41, S96–S99

www.nature.com/bmt

ORIGINAL ARTICLE

Haematopoietic SCT in autoimmune diseases in children: rationale and new perspectives

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The possible role of haematopoietic SCT (HSCT) for the treatment of severe autoimmune diseases was originally supported by animal experiments and remission of concomitant autoimmune diseases in patients undergoing transplantation for haematological disorders. Since 1996, over 100 procedures were performed in children with different severe autoimmune diseases such as juvenile idiopathic arthritis, systemic lupus erythematosus, systemic sclerosis, immune cytopaenias and Crohn's disease. This review tries to summarize the published data on efficacy and toxicity of HSCT in this group of patients.
Bone Marrow Transplantation (2008) **41,** S96–S99; doi:10.1038/bmt.2008.64
Keywords: haematopoietic SCT; autoimmune disease; children

Introduction

Autoimmune diseases (ADs) affect around 3–5% of the general population.[1,2] The majority of ADs are controlled by conventional therapies acting on the immune system. Such treatments are rarely curative and they may contribute to long-term morbidity and mortality. Moreover, there is a hard core of refractory/relapsing treatment-resistant forms of ADs for which the term 'malignant ADs' has been appropriately proposed.[3,4]

Studies from animal models showed that both allo-SCT and auto-SCT were able to cure some spontaneous and induced ADs.[5–7] In human beings, it has been documented that the transfer of a broad range of ADs from donor to recipient may occur, including diabetes mellitus, thyroiditis, psoriasis, myasthaenia gravis, coeliac disease, ulcerative colitis and immune thrombocytopaenic purpura.[8] A few anecdotal reports showed that allogeneic haematopoietic SCT (allo-HSCT) and autologous haematopoietic SCT (auto-HSCT) performed for a coexisting haematological condition either succeeded in curing patients with rheumatoid arthritis and other autoimmune disorders, or resulted in long-lasting remission.[9–11]

Allogeneic transplant is believed to be effective by reducing self-reactive lymphocytes during the conditioning regimen, hence eliminating residual immune cells by a graft-vs-autoimmune effect of the healthy donor-derived immune system. On the other hand, the efficacy of auto-HSCT may result from a similar ablation of self-reactive lymphocytes during conditioning, followed by the induction of self-tolerance thanks to the re-education of HSCT-derived lymphocytes.[12]

On the basis of these preliminary data, under the auspices of EBMT and the European League against Rheumatism (EULAR), in 1996 the consensus guidelines about the use of stem cell therapy in ADs were published and the International Autoimmune Disease Stem Cell Project Database was established.

By 2006, this European database has registered almost 600 patients, the majority of whom have been treated with auto-HSCT. Fifteen per cent of these patients were children receiving an SCT for a variety of conditions (Table 1). Juvenile idiopathic arthritis was the main condition for an auto-SCT, whereas the immune cytopaenias were prevalent in the allogeneic group. A large number of phase I/II studies have evaluated the safety and efficacy of HSCT in specific disease groups such as juvenile idiopathic arthritis, systemic sclerosis, systemic lupus erythematosus and autoimmune cytopaenias.[13–17] Only two published studies evaluated the safety and efficacy of HSCT in a cohort of children.[13,17]

The aim of this review is to try to summarize the data, focusing on the largest disease groups.

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis is the most common rheumatic disease in children and a major cause of disability; in 5–10% of children with the systemic and polyarticular onset forms, the disease is refractory to non-steroidal anti-inflammatory drugs and immunosuppressive drugs such as MTX and corticosteroids with an estimated mortality in the whole group of 2–4%.[18,19] More recently, the introduction of biological agents such as anti-TNF treatment and anti-IL-6 receptor treatment had a major impact on the

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Table 1 HSCT for autoimmune disease in children reported in the EBMT database

Transplant type	
Autologous	99
Allogeneic	21
Rheumatological	
Juvenile idiopathic arthritis	52
Systemic lupus erythematosus	17
Systemic sclerosis	5
Wegener's granulomatosis	2
Vasculitis	2
Mixed connective tissue disease	3
Haematological	
Autoimmune haemolytic anaemia	15
Idiopathic thrombocytopaenic purpura	3
Evan's syndrome	3
Pure red cell aplasia	2
Gastrointestinal	
Inflammatory bowel disease	5
Autoimmune enteropathy	1
Others	
Ipex	1
Multiple sclerosis	3
Unspecified	6

Abbreviation: HSCT = haematopoietic SCT.

outcome of children with polyarticular form but seems less effective in active systemic diseases.[20,21]

Since 1997, the auto-HSCT has been applied in patients with refractory polyarticular and systemic juvenile idiopathic arthritis, and 52 cases were reported and registered in the EBMT database. The more extensive retrospective analysis included 34 patients transplanted after a conditioning regimen based on antithymocyte globulin (ATG), CY with or without low-dose TBI, 4 Gy, and T-cell depletion.[13] In all, 53% of patients after a follow-up of 12–60 months achieved a complete drug-free remission, while other six patients (18%) showed a partial response. The incidence of infectious complications was high with three children who died of a haemophagocytic syndrome with a TRM of 9%. The other smaller published experience included five patients with systemic and polyarticular form transplanted after a milder conditioning regimen based on ATG, CY or fludarabine followed by long-term CYA after the transplant; the transplant-related toxicity was mild but all patients, after an initial CR or PR, relapsed within 12 months.[17]

Systemic lupus erythematosus

Systemic lupus erythematosus is a multisystem inflammatory disorder that, before the advent of immunosuppressive medications, was generally fatal. After the introduction of more aggressive anti-inflammatory and immunosuppressive therapies such as monthly CY or mycophenolate mofetil, the 5-year survival rate improved up to 90% in children. Despite these advances, some patients continue to have significant morbidity and mortality due to visceral involvement.[22–24]

Since 1997, 17 paediatric patients with severe and refractory systemic lupus erythematosus received an auto-SCT and were registered in the EBMT database. Some of them were included in a recent European retrospective survey carried out by EBMT/EULAR registry. After a conditioning regimen employing CY, ATG and TLI with purging in half of the cases, a persistent remission of disease activity after a median follow-up of 26 months was achieved in 50% of patients with a TRM of 12%.[15] Other two paediatric cases were published more recently, one of them maintaining a CR of disease after 4 years, while the other patient relapsed 9 months after the procedure.[25]

Systemic sclerosis

Juvenile systemic sclerosis is a rare multisystem disorder characterized by skin and visceral (lung, gastrointestinal, cardiovascular and renal) fibrosis as a consequence of excessive collagen deposition. Although the outcome of the juvenile systemic sclerosis is better than that of the adult forms, patients with extensive skin and pulmonary involvement showed a 5-year mortality of 10%.[26,27] Several immunosuppressive drugs such as corticosteroids, MTX, CY and D-penicillamine were used but none has been proved to prevent disease progression. Given its autoimmune pathogenesis, juvenile systemic sclerosis has been a candidate for evaluation of experimental therapies as auto-HSCT.

The data from five patients registered in the EBMT database were recently published in a larger group.[14] The median age at the time of HSCT was 12 years. All patients presented a severe lung disease at inclusion and the conditioning regimen was CY-based with purging. After a median follow-up of 37.5 months (range: 13–67), all five children were alive and three of them in CR.

Immune cytopaenia

Different autoimmune haematological cytopaenias, not responsive to conventional treatments, such as AIHA (autoimmune haemolytic anaemia), ITP (immune thrombocytopaenia), the combination of both (Evans's syndrome) and PRCA (pure red cell aplasia), received an HSCT. Until now, 23 children suffering for an immune cytopaenias had been registered in the EBMT registry, 13 of them receiving an allo-HSCT, whereas 10 an auto-HSCT. Some of them were included in a recent retrospective analysis;[16] the PFS in the entire cohort was 45% in recipients of an autologous transplant and 78% in recipients of an allogeneic transplant. A retrospective analysis on the paediatric group is ongoing. Data published are available for seven children; three patients received an allo-HSCT (one PRCA, one AIHA and one Evans's syndrome) of whom two continued in CR and one died of hepatitis 9 months after the transplant in CR.[28–30] The remaining four patients received an auto-HSCT after a conditioning regimen with CY and ATG (two AIHA, one ITP and one PRCA), and only one maintains a CR 20 months post autograft.[17,31,32]

Crohn's disease

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract, which commonly affects adolescents and young adults with a prevalence in paediatric age of 16/100 000.[33] The activity of the disease can be controlled by the use of immunosuppressive drugs, biological disease modifiers and surgical intervention; however, there is a subset of patients in whom the disease presented an aggressive course with a reduced life expectancy. Genetic studies suggest that in Crohn's disease there may be several defects in the haematolymphatic cells, and BM-derived cells are involved in the healing process following intestinal injury and may contribute to various components of the mucosa including myofibroblasts and endothelium.[34,35]

Recently, the Chicago Group reported a study in which 12 patients with refractory Crohn's disease underwent an auto-HSCT after a conditioning regimen with CY and ATG plus T-cell depletion. Two of them were children and both, after a follow-up of 7 and 15 months, are in CR without any need for further treatments.[36]

Discussion

Most patients were selected for HSCT because they were considered refractory to all available conventional therapy, and this procedure can only be presently considered as salvage therapy. The number of transplants for ADs in children is constantly reducing in the past few years, especially because of the recent introduction of targeted therapy. In spite of this as the current trend, HSCT has the ability to intensify conventional immunosuppressive treatment (for example, CY), to re-induce an immunological tolerance in an aberrant immune network and to introduce the concept of a stable cure of AD when the patient's autoreactive immunocompetent cells are replaced by healthy, non-autoreactive cells. Of the three approaches discussed here—auto-HSCT rescue following intense immunosuppression, intense immunosuppression alone and allo-HSCT—the last approach is theoretically the most promising.

Auto-SCT, which originated from the animal experiments by van Bekkum,[7] is being utilized as a possible therapy for severe refractory ADs, because of its lower TRM and greater feasibility. In terms of efficacy, half of the patients presented in this review—with a very severe course of disease—achieved a complete and sustained remission of disease, and a part of them—after a relapse—showed restored sensitivity to previously ineffective therapies. In the first years, the TRM was unacceptably high possibly because the patient selection was limited to children with impaired vital organ function, but the later results seem to indicate a learning curve, which is probably the result of better selection.[8] It is still uncertain whether the mechanism of action in the autologous setting is essentially immunosuppressive without the need of stem cell rescue or, as recently published, auto-HSCT has the potential to induce immunological self-tolerance by reprogramming autoreactive cells to a tolerant phenotype and restoring the CD4 + CD25 + immune regulatory network.[37]

Preliminary data on allo-HSCT appear encouraging regarding the potential for cure not only because it confers a new healthy immune system, but also because of the additional advantage of eradication of residual recipient autoreactive cells by a well-documented graft-vs-autoimmunity reaction.[38] Of course, a recent demonstration of a catastrophic relapse of Evan's syndrome 5 years after allo-SCT notwithstanding full-donor chimaerism should be kept in mind.[39]

Finally, prospective randomized phase III trials such as ASTIS (systemic sclerosis), ASTIMS (multiple sclerosis) and ASTIRA (rheumatoid arthritis) in adults are needed in the paediatric field to address the role of HSCT for AD in children.

Acknowledgements

We thank Professor Alberto Marmont for his suggestions and comments on the paper and Dr Riccardo Saccardi, Chair of the EBMT Autoimmune Disease Working Party, for supplying details of the EBMT database.

Conflict of interest

None of the authors declared any financial interests.

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