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Treatment of refractory autoimmune diseases with autologous stem cell transplantation: focus on juvenile idiopathic arthritis

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Summary:

Autologous stem cell transplantation (ASCT) can be performed in a variety of refractory autoimmune diseases. A retrospective multicenter analysis is presented to evaluate safety and efficacy of ASCT for refractory juvenile idiopathic arthritis. In all, 18 of the 34 patients (53%) with a follow-up of 12 to 60 months achieved a drug-free complete remission. There were three cases (9%) of transplant-related mortality and two cases of disease-related mortality (6%). Infectious complications were seen frequently. We propose adjustments in future protocols to reduce this mortality in this high-risk patient group.

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Since the mid-1990s, autologous stem cell transplantation is performed for a variety of autoimmune diseases, such as RA, MS, systemic sclerosis and SLE. This treatment was initiated by the observations in patients with coincidental autoimmune disease transplanted for conventional indications, as well as animal models showing the efficacy of autologous stem cell transplantation (ASCT) in adjuvant arthritis in Buffalo rats.[1,2] To date, more than 530 patients with various autoimmune disorders underwent an auto-SCT since 1996 (source: EBMT/EULAR database). The major disease categories are summarized in Table 1. Among them, a very limited number of children. This article summarizes the experience so far with auto-SCT for pediatric rheumatic diseases.

In recent years, the treatment of children with juvenile idiopathic arthritis (JIA) who were unresponsive to conventional antirheumatic drugs has been intensified considerably. Potent immunosuppressive drugs have been introduced earlier in attempts to suppress joint inflammation in those children who did not respond to nonsteroidal antiinflammatory drugs . However, despite the use of a variety of drugs including high-dose intravenous methylprednisolone, methotrexate given parenterally in increasingly high doses, and cyclophosphamide both orally and intravenously, most pediatric rheumatologists have looked after children with JIA, particularly systemic JIA, who have not responded adequately to such treatment.[3] Clearly, the introduction of biological agents (such as antitumor necrosis factor (TNF) treatment and anti-IL6 receptor treatment) for the treatment of DMARD-resistant JIA has been proven to be of great value.[4,5] Early experience with the anti-TNF drugs also suggests that a significant proportion of children with systemic JIA are likely to remain resistant to these therapies.[6] Children with this refractory form of JIA not only develop severe morbidity, and significantly impaired quality of life, both from the disease, and from drug toxicities, but they have a significantly increased mortality rate.[7,8]

If a child with JIA continues to have poorly controlled joint inflammation despite consistent pharmacological interventions, the child is a candidate for experimental therapies. However, the outcome of such therapies is very difficult to assess unless the child's treatment is undertaken in a center that can provide a multidisciplinary approach. Although the clinical end points are more difficult to assess for children with arthritis than for those with cancer, the clinical outcome parameters and the increasing variety and number of new drugs make a similar approach not only feasible but essential.[9,10] Since 1997, ASCT has been applied as an experimental procedure in more than 50 children with refractory JIA.[11] We here show follow-up data on 34 children with JIA, treated with ASCT in order to evaluate feasibility, safety and efficacy.

Data collected from 11 European pediatric SCT centers were immunological reconstitution, complications and key rheumatological parameters. The clinical follow-up of the children ranged from 12 to 48 months. Of the 34 patients, 18 achieved a drug-free complete remission lasting up to 5 years from transplant.[11] Seven of these patients had previously failed treatment with anti-TNF therapy. Six of the 34 patients showed a partial response (ranging from 30 to 70%) and seven of the 34 patients showed a complete relapse of disease.[11] Infectious complications were seen frequently. There were three cases of transplant-related mortality and two cases of disease-related mortality.[12] It

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Table 1 Registries for SCT for autoimmune diseases

	EBMT	*IBMTR/ABMTR*[a]
Transplant type		
Autologous	521	186
Allogeneic	26	23
Indication		
Neurological		
Multiple sclerosis	161	77
Other	8	6
Rheumatological		
Systemic sclerosis	88	32
Systemic lupus erythematosis	66	55
Rheumatoid arthritis	72	6
JIA	54	2
Dermatomyositis	7	
Wegener's granulomatosis	6	
Bechet's syndrome	5	1
Mixed connective tissue disease	4	
Other	13	5
Hematological		
Idiopathic thrombocytopenic purpura	12	6
Autoimmune hemolytic anemia	5	
Pure red cell aplasia	4	
Thrombotic thrombocytopenic purpura	3	
Other	3	4
Miscellaneous		
Inflammatory bowel disease	5	10
Others	6	5

[a]Data presented were obtained from the statistical center of the International Bone Marrow Transplant Registry and Autologous Blood and Marrow Transplant Registry. The analysis has not been reviewed or approved by the advisory or scientific committees of the IBMTR and ABMTR.

was concluded that performing a transplant during active systemic phase of the disease or certain infections could induce episodes of severe hemophagocytosis (also referred to as macrophage activation syndrome, MAS). What we do not know is why especially patients with systemic JIA are at risk for episodes of reactive hemophagocytosis.[13] It is well known that hemophagocytosis occurs during (viral) infections or in patients with rheumatic diseases, especially systemic-onset JIA (SoJIA). Over the past 30 years, a variety of case reports describes the occurrence of hemophagocytosis in SoJIA.[14,15] Of interest, often such an episode seemed to be induced by drugs such as salazopyrin, methotrexate or intramuscular gold.[16–19] Recently, we experienced an episode of hemophagocytosis in three patients with SoJIA who received fludarabine as part of the conditioning protocol (Vastert *et al*, manuscript in preparation).

It must be stressed that this complication accounts for the significant part of the mortality that occurs in SoJIA, and further research in this area is warranted. Earlier, we and others focused on deficient cytotoxic mechanisms such as a decreased expression of perforin in cytotoxic T cells and NK cells, but the pathophysiological significance of this observation still remains to be elucidated.[20,21]

The EBMT-working parties for autoimmune diseases and inborn errors decided to continue to explore the use of ASCT in children with treatment refractory polyarticulate or SoJIA. To achieve a joint approach, we will put forward a protocol that includes antithymocyte globulin and cyclophosphamide followed by fluadarabine. To avoid hemophagocytosis, this will be performed under high dosages of corticosteroids and cyclosporine. Detailed protocol guidelines will be discussed at the next EBMT-working party.

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