

Treatment of Refractory Juvenile Idiopathic Arthritis



In recent years, treatment of childhood rheumatic diseases has been intensified considerably. Potent immunosuppressive or cytostatic drugs have been introduced earlier to suppress the disease in children that did not respond to nonsteroidal antiinflammatory drugs (NSAID). However, despite the use of high dose regimens of methotrexate (MTX), methylprednisolone, and cyclophosphamide pulses, many pediatric rheumatologists have seen patients with systemic juvenile idiopathic arthritis (JIA) who did not respond to such treatments. These children suffer ongoing disease activity with pain, severe joint destruction, and drug toxicity. In many cases there is considerable mortality and a poor quality of life.

ANTI-TUMOR NECROSIS FACTOR RECEPTOR TREATMENT

Recently, 2 new treatments have been described for resistant JIA. The introduction of anti-tumor necrosis factor receptor (TNFr) treatment appears to have had a major effect on outcome of children with polyarticular JIA who were unresponsive to MTX, with a persistent response of up to 80%¹. Use of anti-TNFr in children with systemic disease has been discussed extensively at pediatric rheumatology meetings and the general impression (reflecting experience in some 40 patients with systemic JIA, treated for more than 4 months) is that in active systemic disease this treatment is less effective, with a clear response in a minority of patients only. So there will remain a group of children with (mainly) systemic JIA that do very poorly and end up severely handicapped. This group also probably has an increased mortality risk, although studies are lacking to ascertain the risk. A large and experienced facility like the pediatric rheumatology department of Sick Children's Hospital in Toronto estimates a mortality risk of 3% in this group (R. Laxer, personal communication).

AUTOLOGOUS HEMOPOIETIC STEM CELL TRANSPLANTATION

Autologous hemopoietic stem cell transplantation (auto-SCT) has been applied to adults with multiple sclerosis, systemic sclerosis, rheumatoid arthritis (RA), and systemic lupus erythematosus and children with JIA². The first use of

auto-SCT in JIA was in children with the most severe and longstanding systemic disease, with much irreversible erosive joint destruction already present³. In these patients, the results of auto-SCT were nevertheless striking, with a prolonged drug-free followup of 3 to 39 months in 9 of the 14 children treated in the Netherlands⁴. Using the core criteria for improvement of RA, a similar set of criteria was developed for JIA⁵. Eight of 14 patients showed a drug-free improvement of more than 50% of their disease following auto-SCT. At present 29 patients with childhood onset JIA have been transplanted and registered in the database of the Working Party for Autoimmune Diseases of the European Blood and Marrow Transplantation group (EBMT). A general impression of these data is given in Table 1. Clearly, these children represent the most severe and drug resistant forms of JIA. Some data for JIA are still lacking and this list cannot be viewed as complete. Of the 29 children, 16 were reported to be in "drug-free remission," 8 were in partial remission or relapse for which NSAID or low dose steroids were prescribed, and one was a nonresponder (Table 1). Four patients died. Causes of death were mostly infection associated with aplasia. In 3 of these, hemophagocytosis, a well known complication of systemic JIA, was also present. This was preceded by infections such as Epstein-Barr virus reactivation and disseminated toxoplasmosis. The data pertaining to followup after auto-SCT in these 29 children are still limited and do not permit a detailed analysis of the changes of the core set criteria.

COMPLICATIONS OF AUTO-SCT

Importantly, the above mentioned fatalities indicate the need for careful selection. The experiences also illustrate that this small group of children is also a high risk group for conventional therapy. To be eligible for auto-SCT, children must have failed all available conventional treatment, including anti-TNFr treatment. Patients with chronic infections and existing cardiac toxicity must be excluded. Clearly, children could benefit more from auto-SCT if they could be identified as resistant to conventional treatment early in the course of their disease. They would not be subjected to treatments that were insufficient, destructive joint lesions could be prevented, and, more important, fewer complications of

Table 1. Results after auto-SCT (ASCT) for JIA in European and North American centers.

| Patient | Center | Age at Diagnosis, yrs | Age at ASCT, yrs | TCD (Y/N) | Conditioning | Followup, mo | Outcome | Present Antirheumatic Drugs |
|---------|----------------------|-----------------------|------------------|-----------------------|-----------------------------|--------------|---|-----------------------------|
| 1-11 | Utrecht, Netherlands | 1-7 | 7-14 | CD2/3 (6) CD34 (3) | Cy, ATG, TBI (4 Gy) | 4-36 | 8 remission, 2 partial remission, 1 fatal MAS | Low steroids (2), NSAID (1) |
| 12-14 | Leiden, Netherlands | 2-10 | 4,6,14 | CD2/3 (1) CD34 (2) | Cy, ATG, TBI (4 Gy) | 12-15 | 1 remission, 1 partial remission, 1 fatal MAS | Salazopyrin (1) |
| 15 | Paris, France | 8 | 9 y | CD34 | Cy, ATG | — | Day 18 disseminated toxoplasmosis and fatal MAS | |
| 16,17 | Goteborg, Sweden | | 4-9 | CD2/3 | Cy, ATG, TBI (4 Gy) | 3-10 | Both remission | Low steroids in 1 |
| 18-22 | Trieste, Italy | 3-15 | 8-20 | VCR | Cy, ALG (3) Flu, ALG (2) | 12-36 | Remission 3 Relapse 2 | Etanercept (1), NSAID (1) |
| 23 | Portland, USA | 2 | 10 | CD34 | Cy, ATG, TBI (4 Gy) | 7 | Remission | None |
| 24,25 | Brussels, Belgium | 1-7 | 8, 17 | CD34 | Cy, ATG | 7-19 | Remission | None |
| 26 | Brussels, Belgium | 7 | 15 | CD34 | Cy, ATG | — | Sepsis and fatal cardiac toxicity | — |
| 27,28 | Osaka, Japan | 1-5 | 3-8 | CD34 | Cy, ATG (1) VP16, TT (1) | 4-11 | No response (1) Remission (1) | Low steroids None |
| 29 | Newcastle, UK | 3 | 10 | CD34 | Cy, ATG | 2 | Remission | Low steroids |

CD2/3: negative selection by monoclonal antibodies to CD2 or CD3 positive lymphocytes; CD34: positive selection of CD34+ stem cells; ATG: antithymocyte globulin; TBI: total body irradiation; MAS: macrophage activation syndrome, Cy: cyclophosphamide, ALG: antilymphocyte globulin, Flu: fludarabine, VP16: etoposide, TT: thiotepa. Data were obtained from M. Abinun and H. Foster, Newcastle, England; D. Brinkman, Leiden, The Netherlands; A. Fasth, Goteborg, Sweden; A. Ferster, Brussels, Belgium; K. Keisei, Osaka, Japan; T. Moore, Portland, USA; A.M. Prieur and P. Quartier, Paris, France; M. Rabusin, Trieste, Italy; N. Wulffraat, Utrecht, The Netherlands.

auto-SCT can be expected when auto-SCT is performed at a younger age.

At present, auto-SCT for autoimmune disease is associated with a treatment related mortality of 5-12%, which is a major concern. This raises the question whether any nonmalignant autoimmune disease, whatever the severity, justifies application of an experimental treatment with a 10% mortality risk. In addition, relapses are to be expected, because auto-SCT cannot remove all autoreactive lymphocytes from the body and residual T cells are always present in the reinfused graft.

Allogeneic stem cell transplantation was proposed as an alternative to auto-SCT because healthy, HLA identical donors may not carry putative disease susceptibility genes or autoreactive T lymphocytes. The limited available data do not yet favor allogeneic over autologous transplantation. Remission of autoimmune disorders has been noted in patients receiving allogeneic transplantation primarily for malignancies. However, relapses of the autoimmune disease were also observed, even in patients with 100% donor lymphocytes. In general, allogeneic transplantation is associated with a higher transplant related mortality, especially for patients in poor general condition. Patients with severe autoimmune diseases who have been treated with potent immunosuppressive drugs for a number of years obviously carry a high risk of complications when subjected to allogeneic transplantation.

HOW TO PROCEED?

Two issues must be addressed concerning application of auto-SCT for autoimmune disease. First, selection of patients is critical. Putative selection criteria have been developed at several workshops⁶ and a recent National Institutes of Health meeting in Bethesda, Maryland, USA, in June 2000. For instance, careful cardiac evaluation should be performed for signs of cardiac amyloidosis or drug toxicity. We must try to refine early prediction of a severe course of the disease in individual patients. Possible indicators of poor prognosis in systemic JIA may be the presence of thrombocytosis and persistent fever (or steroid dependency to control fever) at 6 months after the onset of disease⁵. Second, randomized trials are necessary — the best way to study the efficacy of auto-SCT. Given the rarity of such treatment resistant disease, such a trial should be multicenter. A trial should also assess the necessity of T cell depletion of the graft, because its effect has never been proven and it is associated with severe infections. In a later phase, alternative conditioning regimens could be tested, i.e., focusing on the necessity or dosage of total body irradiation (TBI). Existing collaboration between pediatric rheumatology centers in Europe and in North America should make this feasible. It is notable that the present Food and Drug Administration guidelines demand randomization after the initial phase I/II studies. Recently several workshops have set criteria for inclusion and proposed study

protocols⁶. Given the rarity of such severe JIA, joint American-European collaborative trials using standardized protocols are preferred, because then changes to protocols can be based on evidence.

NICO M. WULFFRAAT, MD;
WIETSE KUIS, MD,
Department of Pediatric Immunology,
Suite KC 03.063.0,
Wilhelmina Children's Hospital,
University Medical Centre Utrecht,
PO Box 85090,
3508AB Utrecht, The Netherlands.
E-mail: N.Wulffraat@wkgz.azu.nl

Address reprint requests to Dr. Wulffraat.

REFERENCES

1. Lovell DJ, Giannini EH, Reiff PHA, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. The Pediatric Rheumatology Collaborative Study Group. *New Engl J Med* 2000;342:763-9.
2. Jantunen E, Myllykangas-Luosujärvi R. Stem cell transplantation for treatment of severe autoimmune diseases: current status and future perspectives. *Bone Marrow Transplantation* 2000;25:351-6.
3. Wulffraat NM, van Royen A, Bierings M, Vossen JM, Kuis W. Autologous haemopoietic stem cell transplantation in four patients with refractory juvenile chronic arthritis. *Lancet* 1999;353:550-3.
4. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;40:1202-9.
5. Spiegel LR, Schneider R, Lang BA, et al. Early predictors of poor functional outcome in systemic onset juvenile rheumatoid arthritis — a multicenter cohort study. *Arthritis Rheum* 2000;43:2402-9.
6. Wulffraat NM, Kuis W, Petty RE. Addendum: proposed guidelines for autologous stem cell transplantation in juvenile chronic arthritis. *Rheumatology* 1999;38:777-8.