Rationale for high-dose cyclophosphamide and medium-dose total body irradiation in the conditioning of children with progressive systemic and polyarticular juvenile chronic arthritis before autologous stem cell transplantation

J. M. Vossen, D. M. C. Brinkman, B. Bakker, P. M. Hoogerbrugge and R. ten Cate

Department of Paediatrics, Leiden University Medical Centre, Leiden, The Netherlands

Despite the fact that the aetiology of juvenile chronic arthritis (JCA) is unknown, there is ample indirect evidence of a pivotal role of T cells in the onset and probably also in the maintenance of this autoimmune disease. Notwithstanding adequate first- and second-line anti-rheumatic therapy, systemic-onset JCA and polyarticular JCA will lead to destructive arthritis, growth retardation and severe invalidity in 10–25% of the cases. In order to halt the disease progression in the latter group of JCA patients, a clinical trial was started in order to study the effect of severe immune suppression followed by 'unbiased' immune recovery on the course of the disease. Based on animal studies, showing the regression of adjuvant-induced arthritis by bone marrow transplantation (BMT), both allogeneic and T-cell-depleted autologous BMT [1, 2], a study protocol for autologous stem cell transplantation in children with severe progressive systemic and polyarticular JCA was drafted.

There are two conditions which have to be fulfilled in order for autologous stem cell transplantation to possibly be effective in the treatment of JCA, i.e. first, the conditioning has to wipe out the (dysfunctioning) immunological memory and, second, the re-infused haematopoietic stem cell suspension has to be purged of mature 'memory' T cells. In order to achieve these goals, the following procedure has been proposed: a pre-treatment regimen comparable to the one in use for allogeneic BMT of transfusion-sensitized patients with severe aplastic anaemia (frequently also an autoimmune disease), followed by the re-infusion of a T-cell-depleted (TCD) autologous BMT, i.e. containing \( \leq 10^4 \) T cells/kg body weight of the recipient (see the scheme in Fig. 1).

Such a conditioning suppresses host memory T-cell immunity severely, but is supposed not to be myeloablative. The short-term effect may be the occurrence of viral infections or reactivations, especially with herpes viruses. The possible long-term side-effects may be a slightly increased risk for premature cataract formation and some effect on spermatogenesis in boys. Our experience so far with this pre-treatment in eight children, who received an allogeneic BMT for severe aplastic anaemia, four of whom were prepubertal at BMT and reached final height at evaluation [3], is as follows: no adverse effect has been observed on physical growth, all graft recipients had a normal pubertal development, but the boys had a somewhat decreased testicular volume, indicating germ cell damage. Both the boys and the girls showed normal function of the gonads and thyroid gland by endocrinological testing on follow-up. It is still too early to assess fathering/mothering possibilities in this group of ex-BMT recipients. A slight increase in secondary malignancies has to be expected, as was also seen after immunosuppression or allogeneic BMT for severe aplastic anaemia [4]. Although the use of radiation, mostly limited-field irradiation such as total lymphoid irradiation or thoracoabdominal irradiation, was found in that retrospective study to be a strong risk
factor for the development of secondary malignancies following BMT, immunosuppression alone, especially several courses of that therapy, also increased the risk of secondary tumours.

The Dutch cooperative study on the therapeutic effect of autologous TCD-BMT for progressive JCA started recently as a pilot study. After at least 15 JCA patients have been included and followed for \( \geq 2 \) yr, modifications of the autologous stem cell transplant procedure may be introduced. These modifications will then be studied prospectively, preferably in a large international cooperative trial. The following questions might be addressed:

- Can the conditioning be changed, e.g. by substituting fludarabine for TBI as immunosuppressive agent?
- How much T-cell depletion is needed, e.g. should a selective depletion of memory T cells be performed or is the re-infusion of selected CD34-positive (peripheral blood) stem cells a suitable alternative?
- Is it possible to induce tolerance in the recovering ‘naive’ T cells following autologous stem cell transplantation, e.g. by mucosal administration of defined epitopes of self-antigens?

References