Abstract

Objective. In adults, autologous stem cell transplantation (ASCT) has been described recently as a possible treatment for severe autoimmune disease refractory to conventional treatment. We report here the four first children with severe forms of juvenile chronic arthritis (JCA) treated with ASCT.

Methods. We studied three children with systemic JCA and one child with polyarticular JCA. Unprimed bone marrow was harvested 1 month prior to ASCT. T-cell depletion of the graft was performed with CD2 and CD3 antibodies. We used a preparative regimen of antithymocyte globulin (ATG; 20 mg/kg), cyclophosphamide (Cy; 200 mg/kg) and low-dose total body irradiation (TBI; 4 Gy). Methotrexate (MTX) and cyclosporin A (CsA) were stopped before ASCT; prednisone was tapered after 2 months.

Results. After ASCT, our patients showed an anti-inflammatory-drug-free follow-up of 6–18 months with a marked decrease in joint swelling, pain and morning stiffness. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and haemoglobin (Hb) returned to near-normal values within 6 weeks. Despite T-cell depletion, there was a very rapid immune reconstitution. Two patients developed a limited varicella zoster virus (VZV) eruption which was treated by acyclovir.

Keywords: Juvenile chronic arthritis, Refractory, Treatment, Autologous stem cell transplantation.
**Table 1. Clinical characteristics of the JCA patients before ASCT**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age at onset of disease</th>
<th>Onset form</th>
<th>ANA</th>
<th>RF</th>
<th>Treatment</th>
<th>Clinical characteristics</th>
<th>ASCT (age)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1 yr</td>
<td>Systemic JCA</td>
<td>–</td>
<td>–</td>
<td>NSAIDs, corticosteroids, IVIG, MTX, CsA</td>
<td>Erosions, growth disturbance</td>
<td>6 yr, 7 months</td>
<td>18 months</td>
</tr>
<tr>
<td>Female</td>
<td>3 yr</td>
<td>Polyarticular JCA</td>
<td>–</td>
<td>–</td>
<td>NSAIDs, corticosteroids, MTX, CsA</td>
<td>Erosions, growth disturbance</td>
<td>7 yr, 9 months</td>
<td>15 months</td>
</tr>
<tr>
<td>Male</td>
<td>3 yr, 6 months</td>
<td>Systemic JCA</td>
<td>–</td>
<td>–</td>
<td>NSAIDs, corticosteroids, MTX, CsA</td>
<td>Erosions, growth disturbance</td>
<td>11 yr, 2 months</td>
<td>11 months</td>
</tr>
<tr>
<td>Female</td>
<td>5 yr, 3 months</td>
<td>Systemic JCA</td>
<td>–</td>
<td>–</td>
<td>N/A</td>
<td>Erosions, growth disturbance</td>
<td>11 yr</td>
<td>9 months</td>
</tr>
</tbody>
</table>

**Conditioning**

The conditioning regimen prior to ASCT included 4 days of antithymocyte globulin (ATG; IMTIX, Pasteur Mérieux, France) in a dosage of 5 mg/kg daily from day −9 to −6, cyclophosphamide (Cy) in a dose of 50 mg/kg daily from day −5 to −2, and low-dose (4 Gy) single-fraction total body irradiation (TBI) on day −1.

**Results**

The clinical characteristics of the four patients are depicted in Table 1. They were characterized by a refractory chronic arthritis with the occurrence of erosions and growth disturbances of the joints. The duration of disease was >5 yr in all. Laboratory investigations showed increased erythrocyte sedimentation rate (ESR) and a moderate to severe anaemia in all patients.

MTX and CsA were stopped prior to ASCT, and corticosteroids were tapered and stopped 2 months after ASCT. NSAIDs were continued, but in all patients medication could be stopped completely within 6 months.

The recovery of the bone marrow took 20–30 days for neutrophils (>0.5 × 10⁹/l) and 16–35 days for the platelets (>20 × 10⁹/l). The number of T cells and in vitro mitogen responses normalized within 3–6 months.

Within 2 weeks of ASCT, all patients showed a marked improvement, as measured by a decrease in joint swelling, pain and morning stiffness. ESR, C-reactive protein (CRP) and haemoglobin (Hb) normalized within 8 weeks. As measured by child health assessment questionnaires (CHAQ), EPM-ROM and juvenile arthritis functional scores (JAFAS), there is a marked improvement in the functional activities of all children (Table 2). Because of the longer follow-up in the first two patients, a favourable effect of ASCT on growth could already be seen in patients 1 and 2 (Fig. 1).

In general, the ASCT was well tolerated and there were few complications (Table 3).

**Discussion**

The effect of ASCT on signs and symptoms of chronic joint inflammation in four severely affected patients was very favourable. The initial improvement could be explained by the immune suppression of the conditioning regimen, but the duration of the remission, even after recovery of the T cells and T-cell function, is indicative of an immune modulatory effect of ASCT. However,
It is necessary to balance the risk of ASCT against conventional therapy with regard to outcome measurements and toxic side-effects of treatment. In this respect, ASCT still has to be regarded as an experimental therapy for children with severe refractory JCA and other autoimmune diseases. Recent experience in Europe indicates that ASCT for severe autoimmune disease carries a mortality risk of 10%. Therefore, we need consensus on inclusion criteria, conditioning regimen and graft handling. However, the short-term results of ASCT in our four patients are very promising and although the follow-up period is too short, the first impression is that ASCT could be an important weapon in the battle against refractory JCA.

References

4. Slaper-Cortenbach ICM, Admiraal LG, van Leeuwen EF, F. Failure to grow for at least 3 yr preceding the ASCT. Kerr JM, von dem Borne AE, Tettero PAT. Effecfective The arrowhead indicates the age of onset of disease. From the moment of ASCT (BMT, arrow), the patient showed a rapid catch-up growth. Horizontal axis, age in years; vertical axis, length in centimetres.

the follow-up period is too short for definite conclusions. An interesting phenomenon is the occurrence of a benign, oligoarticular synovitis in two of the four patients. This occurred simultaneous with T-cell recovery. The self-limiting character of the synovitis favours the concept of a beneficial immunomodulatory effect post-ASCT. Note that patients 1 and 2 are in complete remission for >12 months in the presence of a fully reconstituted immune system. Whether T-cell depletion of the graft is necessary to sustain remission is not known. Early recurrences of systemic lupus erythematosus by using unmanipulated grafts suggest that T-cell depletion may be essential [5]. The use of TBI in our conditioning regimen is questionable. TBI is very effective in an animal model of arthritis [6, 7], so we included a low-dose TBI in our protocol. By using a low dose, we avoid the negative effects of TBI on growth and maturation [8, 9], although it is not known whether low-dose TBI increases the risk for secondary malignancies [10]. Careful evaluation of these patients is necessary to balance the risk of ASCT against conventional therapy with regard to outcome measurements and toxic side-effects of treatment. In this respect, ASCT still has to be regarded as an experimental therapy for children with severe refractory JCA and other autoimmune diseases. Recent experience in Europe indicates that ASCT for severe autoimmune disease carries a mortality risk of 10%. Therefore, we need consensus on inclusion criteria, conditioning regimen and graft handling. However, the short-term results of ASCT in our four patients are very promising and although the follow-up period is too short, the first impression is that ASCT could be an important weapon in the battle against refractory JCA.

References