T-cell replete haploidentical bone marrow transplantation for X-linked severe combined immunodeficiency

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Dear Sir,

Without definitive therapy, severe combined immunodeficiency (SCID) is invariably fatal within the first two years of life. Allogeneic haematopoietic stem cell transplantation (HSCT) is curative; however, finding a human leukocyte antigen (HLA)-matched sibling donor is challenging. An unrelated donor graft is an alternative option, but it is limited by ethnic-associated disparities, high-costs and a long lag time to procurement. We share our experience in performing T-cell replete haploidentical HSCT (hHSCT) in an infant with T-NK-B+ SCID, leading to full immune reconstitution.

The infant was an only child of an ethnic Malay non-consanguineous couple. He was referred at ten months of age due to recurrent pneumonia, chronic diarrhoea and failure to thrive. His BCG inoculation site was pustular and yielded acid-fast bacilli. Investigations showed markedly reduced T and NK cells with undetectable serum immunoglobulin levels (Table I). Genetic analysis revealed a heterozygous c.270-2A>T mutation in intron 2 of the IL2RG gene (also detected in his mother), confirming the diagnosis of X-linked SCID. Immediate measures included commencement of anti-tuberculosis therapy, as well as intensive nutritional and pulmonary rehabilitation.

Due to the urgency of his circumstances, a T-cell replete 5/10 HLA-mismatched hHSCT was performed using his father’s bone marrow as the stem cell source (nucleated and CD34+ cell dose of $6 \times 10^8$/kg and $1.7 \times 10^9$/kg, respectively). The conditioning regimen consisted of thiotepa 5 mg/kg on Day 7, cyclophosphamide 30 mg/kg on Days 5 and 6, and fludarabine 30 mg/m²/day on Days 2 to 6 with no irradiation. This was a modification of the published Hopkin’s hHSCT protocol. Post transplantation, cyclophosphamide 50 mg/kg/dose was administered on Days +3 and +4. A combination of oral mycophenolate mofetil and cyclosporin A was used as graft-versus-host-disease (GVHD) prophylaxis till Day +90 and Day +180, respectively.
He achieved neutrophil engraftment by Day +10 and platelet engraftment on Day +11. Lineage-specific chimerism analysis demonstrated full donor T-cell engraftment by Day +46. Control of GVHD was challenging, as he developed acute GVHD of the skin (Stage 3) and gut (Stage 1) on Day +12 and Day +53, respectively. He also developed severe pneumonitis on Day +65, which required mechanical ventilation for two days and bi-level positive airway pressure support for three weeks. Tracheal secretions were repeatedly sterile, while polymerase chain reaction screening for adenovirus, influenza and cytomegalovirus were negative.

Despite empirical broad-spectrum antibiotics, micafungin and cidofovir, the child’s respiratory symptoms did not abate. A presumptive diagnosis of GVHD of the lungs was made and pneumonitis resolved after three weeks of prednisolone and cyclophosphamide pulse of 30 mg/kg on Days +105 and +106. He was finally discharged from the ward on Day +149 with no re-admissions for illness. Currently, 28 months post hHSCT, he remains completely well with no evidence of GVHD.

Table I. Immune profile prior to and after bone marrow transplantation (BMT).

<table>
<thead>
<tr>
<th>Immune profile</th>
<th>Normal range for age</th>
<th>Pre-BMT</th>
<th>Day +280</th>
<th>Day +783</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan T cells (cells/µL)</td>
<td>800 – 3,000</td>
<td>445</td>
<td>2,756</td>
<td>6,675</td>
</tr>
<tr>
<td>CD4+ cells (cells/µL)</td>
<td>600 – 1,900</td>
<td>291</td>
<td>1,665</td>
<td>1,682</td>
</tr>
<tr>
<td>CD8+ cells (cells/µL)</td>
<td>200 – 1,200</td>
<td>81</td>
<td>1,087</td>
<td>4,080</td>
</tr>
<tr>
<td>NK cells (cells/µL)</td>
<td>150 – 850</td>
<td>127</td>
<td>321</td>
<td>161</td>
</tr>
<tr>
<td>Pan B cells (cells/µL)</td>
<td>600 – 2,000</td>
<td>2297</td>
<td>1,272</td>
<td>1,011</td>
</tr>
<tr>
<td>Immunoglobulin G (mg/dL)</td>
<td>&gt; 400</td>
<td>&lt; 6</td>
<td>503</td>
<td>419</td>
</tr>
<tr>
<td>Immunoglobulin A (mg/dL)</td>
<td>&gt; 23</td>
<td>&lt; 23</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Immunoglobulin M (mg/dL)</td>
<td>&gt; 17</td>
<td>&lt; 17</td>
<td>27</td>
<td>92</td>
</tr>
</tbody>
</table>

Although the first HSCT to correct SCID was performed nearly 50 years ago, the optimal transplantation preparative therapy or any at all remains controversial. In this child’s case, a reduced-intensity conditioning regimen was chosen to achieve a balance between ensuring engraftment while avoiding a flare-up of his underlying morbidities. T-cell depleted
hHSCT is currently the treatment of choice for infants with SCID who lack an HLA-matched donor.\(^{(3)}\) However, the high cost and expertise required to engineer the graft preclude this technique in countries with limited resources. Our case illustrates that hHSCT using unmanipulated T-cell replete bone marrow is a feasible method to cure infants with SCID.

Yours sincerely,

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REFERENCES

