Bone Marrow Transplantation in Major Histocompatibility Complex Class II Deficiency: A Single-Center Study of 19 Patients

By Christoph Klein, Marina Cavazzana-Calvo, Françoise Le Deist, Nada Jabado, Malika Benkerrou, Stéphane Blanche, Barbara Lisowska-Gros Pierre, Claude Griscelli, and Alain Fischer

Major histocompatibility complex (MHC) class II deficiency (bare lymphocyte syndrome) is a rare inborn error of the immune system characterized by impaired antigen presentation and combined immunodeficiency. It causes severe and unrelenting infections leading to progressive liver and lung dysfunctions and death during childhood. As in other combined immunodeficiency disorders, bone marrow transplantation (BMT) is considered the treatment of choice for MHC class II deficiency. We analyzed the files of 19 patients who have undergone BMT in our center. Of the 7 patients who underwent HLA-identical BMT, 3 died in the immediate post-transplant period of severe viral infections, whereas the remaining 4 were cured, with recovery of normal immune functions. Of the 12 patients who underwent HLA-haplidentical BMT, 3 were cured, 1 was improved by partial engraftment, 7 died of infectious complications due to graft failure or rejection, and 1 is still immunodeficient because of engraftment failure. A favorable outcome in the HLA-nonidentical BMT group was associated with an age of less than 2 years at the time of transplantation. All the patients with stable long-term engraftment had persistently low CD4 counts after transplantation (105 to 650/ml at last follow up), but no clear susceptibility to opportunistic infections despite persisting MHC class II deficiency on thymic epithelium and other nonhematopoietic cells. We conclude that HLA-identical and -haplidentical BMT can cure MHC class II deficiency, although the success rate of haplidentical BMT is lower than that in other combined immunodeficiency syndromes. HLA-haplidentical BMT should preferably be performed in the first 2 years of life, before the acquisition of chronic virus carriage and sequelae of infections.

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PATIENTS, MATERIALS, AND METHODS

Patients

Nineteen children with MHC class II deficiency underwent BMT at the Hôpital Necker-Enfants Malades from April 1981 through June 1993. All received transplants from related donors, who were HLA-matched in 7 cases. Extended specificity serotyping and genotyping for HLA A, B, and DR antigens were applied to potential transplant recipients and their family members. Age at BMT ranged from 6 months to 6 years. Diagnosis was based on deficient HLA class II expression on peripheral blood monocytes, B cells, and phytohemagglutinin (PHA) activated T cells. The cut-off date for the analysis was December 1, 1993.

Treatment Regimen

The conditioning regimens are depicted in Table 1. In HLA-compatible BMT, graft-versus-host disease (GVHD) prophylaxis consisted of methotrexate (10 mg/m²) on days 1, 3, 6, and 11 and cyclosporine for a total of 180 days, except for patient no. 1, who received only methotrexate. The mean number of infused mononuclear cells was 3 × 10⁹/kg (range, 0.6 to 6.2 × 10⁹/kg).

In HLA-mismatched BMT, the conditioning regimen was further reinforced by the infusion of 0.2 mg/kg/day of a monoclonal anti-LFA-1 antibody (25-3 murine IgGl specific for the LFA-1α subunit [CD11a]) from day –3 to day +6 from 1987 onwards, except for patient no. 7, who received 0.1 mg/kg/d of anti-LFA-1 antibody on 5 occasions. From 1991 onwards, a combination of anti-LFA-1 antibody (0.2 mg/kg/d on days –3 to +10) and a monoclonal anti-CD2 antibody (murine BE2, isotype IgG2b; 0.2 mg/kg/d on days –2 to +11) was administered (patients no. 14, 15, 16, 18, and 19). GVHD prophylaxis was based on graft T-cell depletion by E-rosetting or by treatment with Campath-1M antibody (Dr. G. Hale, Cambridge, UK) plus human complement, according to the protocol. The residual T-cell content of the infused marrow was always less than 1.1 × 10⁷ T cells/kg recipient body weight, based on limiting dilution analysis after expansion in interleukin-2 (IL-2)–conditioned medium. Patients no. 10 and 11 received nondepleted donor marrow. In the case of T-cell depletion by E-rosetting, cyclosporine was administered intravenously (3 mg/kg/d) starting on day 0 before marrow infusion until day 60. Doses were adjusted according to GVHD severity and renal or other toxicity. Other treatments of GVHD included corticosteroids and anti–IL-2 receptor monoclonal antibodies.

Patients were infused with a mean of 3.6 × 10⁹ (range, 0.5 to

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Table 1. Conditioning Regimens

<table>
<thead>
<tr>
<th>I. HLA-compatible BMT</th>
<th>II. HLA-mismatched BMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cyclophosphamide (50 mg/kg)</td>
<td>4. Busulfan (20 mg/kg; 16 mg/kg if age &gt;6 yr)</td>
</tr>
<tr>
<td>2. Cyclophosphamide (50 mg/kg)</td>
<td>5. Busulfan (20 mg/kg; 16 mg/kg if age &gt;6 yr)</td>
</tr>
<tr>
<td>CCNU (300 mg/m²)</td>
<td>Cyclophosphamide (200 mg/kg)</td>
</tr>
<tr>
<td>Procarbazine (280 mg/kg)</td>
<td>Anti-LFA-1 antibody</td>
</tr>
<tr>
<td>Antilymphocyte serum</td>
<td>Anti-CD2 antibody</td>
</tr>
<tr>
<td>3. Busulfan (20 mg/kg)</td>
<td>Cyclophosphamide (200 mg/kg)</td>
</tr>
</tbody>
</table>

Supportive Care

Patients were placed in a sterile isolator (Isoconcept, Paris, France) or in isolation rooms with laminar airflow. All patients received gut decontamination, and broad-spectrum antibiotic and antifungal prophylaxis. Patients were administered empirically for episodes of fever. Irradiated red blood cells and platelets were transfused as needed. If evidence of cytomegalovirus (CMV) infection was found before BMT in the donor (serology) or recipient (serology and/or culture of or polymerase chain reaction), acyclovir (1,500 mg/m²/d) was administered from day 0 to 60. Patients with no evidence of CMV infection received blood components from CMV-negative donors. Intravenous immune globulin was administered prophylactically (200 mg/kg/wk) until reconstitution of endogenous immune globulin production. Patient no. 18 also received intrathecal anti-herpesvirus-enriched immune globulin for chronic enterovirus meningitis.

Assessment of Engraftment and GVHD

Engraftment of donor cells was confirmed by testing for HLA-DR expression on peripheral B cells, monocytes, and PHA-activated T cells. Karyotyping in case of sex mismatch, erythrocyte phenotyping, and chimerism analysis by means of restriction fragment length polymorphism (RFLP) on DNA extracted from peripheral mononuclear cells served as additional engraftment markers. The clinical diagnosis of GVHD was confirmed by appropriate biopsies and graded according to Glucksberg et al.18. Lympocytes populations were determined by immunofluorescence with T- and B-cell-specific monoclonal antibodies. Mitogen, antigen (Candida albicans, tetanus toxoid, and CMV), and allogeneic cell-induced lymphocyte proliferation tests were performed as previously described.19

RESULTS

Pretransplant clinical and immunologic characteristics of the 19 patients are shown in Table 2. Chronic enteritis (16 cases) and respiratory tract infections (18 cases) were the hallmarks of the clinical presentation. Hepatitis and/or cholangitis occurred in 10 cases. Meningoencephalitis was diagnosed in 2 cases before BMT. Thirteen patients had persistent viral infections, a major cause of death in MHC class II deficiency. Four patients had slight CD3 lymphopenia, and 14 of 17 patients tested had reduced CD4+ cell counts. Most patients had elevated CD8+ cell counts, but 2 patients had evidence of CD8 lymphopenia.20 HLA-DR expression was, by definition, absent or low. Patients with residual DR expression had no milder clinical presentation. All patients had positive lymphocyte stimulation tests with PHA and negative stimulation tests with antigens. Nine of 11 evaluable patients had hypogammaglobulinemia and IgA levels were reduced in 16 patients and normal in 3, whereas IgM levels were reduced in 14 patients, normal in 4, and increased in 1. Three patients fell into complementation group A, 10 patients into group B, and 6 patients could not be classified. However, neither residual DR expression nor clinical manifestation correlated strictly with the complementation group.

As shown in Table 3, 7 patients received HLA-identical transplants and 12 patients received HLA-haploidentical transplants. Six patients required more than one BMT procedure, owing to engraftment failure. The median age at the time of the first transplant was 27 months in the HLA-identical group and 34 months in the HLA nonidentical group. Eight patients are alive 6 months to 11 years post-BMT, with a functional graft (median follow-up, 50 months).

Engraftment

Engraftment could be evaluated in 18 patients (Tables 3 and 4). Of the 7 patients who received HLA-identical BMT, 3 had initial signs of mixed hematopoietic chimerism but died from infectious complications. Four patients had stable long-term engraftment, with 3 showing full chimerism and 1 (patient no. 2) showing partial engraftment with less than 50% of donor-derived B cells and monocytes. Stable long-term engraftment occurred in only 3 patients who underwent nonidentical BMT. All 3 patients were less than 2 years old at the time of transplantation. In this group, 1 patient (no. 10) had mixed and 2 (nos. 14 and 19) had full hematopoietic chimerism. Another patient (no. 11) had full chimerism but died 3 months post-BMT of severe GVHD and viral infections. One patient (no. 8) had partial T-cell and complete B-cell engraftment with normal production of specific antibodies. However, five years after BMT, she only has 2% of donor B cells. One patient (no. 9) transiently achieved full T-cell function, but gradually rejected the graft over 5 years. Interestingly, full hematopoietic chimerism was only observed after introduction of a protocol using anti-LFA-1 and anti-CD2 antibodies to reduce engraftment failures. No engraftment occurred in 6 patients, despite up to three transplantation attempts; only one of the five Camaphath-depleted grafts (patient no. 9) resulted in engraftment, although the transplant was gradually lost.

Two patients developed stage 3 GVHD, whereas mild to moderate GVHD (stage 2) occurred in 10 cases. No cases of chronic GVHD occurred.

Immunologic Reconstitution

T-cell reconstitution. T-cell reconstitution was confirmed in 6 patients by the presence of HLA-DR expression...
**Table 2. Immunologic and Clinical Characteristics Pre-BMT**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Complementation Group</th>
<th>Age</th>
<th>Lymphocyte Counts (CD3, CD4, CD8)</th>
<th>DR Expression (%)</th>
<th>Ig Serum Level (g/L)</th>
<th>Antibody Production in Response to Immunization</th>
<th>Clinical Findings</th>
<th>Virus Isolated</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>ND</td>
<td>8 mo</td>
<td>ND 4,470 ND 2,750 ND 2,460 ND</td>
<td>B 1 1.86</td>
<td>NE</td>
<td>+</td>
<td>Meningoencephalitis</td>
<td>Enterovirus</td>
</tr>
<tr>
<td>2</td>
<td>ND</td>
<td>10 mo</td>
<td>ND 3,370 1,830 ND 590 ND 1,500 ND</td>
<td>B 1 0.34</td>
<td>NE</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>ND</td>
<td>5 yr 2 mo</td>
<td>2,750 700 1,830 0-6 0</td>
<td>B 1 3.13</td>
<td>NE</td>
<td>+</td>
<td>-</td>
<td>CMV</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>21 mo</td>
<td>920 530 590 0 0</td>
<td>NE 1.97</td>
<td>NE</td>
<td>+</td>
<td>-</td>
<td>Enterovirus</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>6 mo</td>
<td>2,460 1,080 1,500 0 0</td>
<td>NE 8.0</td>
<td>NE</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>ND</td>
<td>8 mo</td>
<td>2,500 1,290 1,400 0 0</td>
<td>NE 8.0</td>
<td>NE</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>9 mo</td>
<td>1,760 500 1,300 0 0</td>
<td>NE 2.66</td>
<td>NE</td>
<td>+</td>
<td>Meningoencephalitis</td>
<td>Enterovirus</td>
</tr>
<tr>
<td>8</td>
<td>B</td>
<td>23 mo</td>
<td>5,400 720 4,680 0 0</td>
<td>NE 5.8</td>
<td>NE</td>
<td>+</td>
<td>Sepsis</td>
<td>CMV, enterovirus</td>
</tr>
<tr>
<td>9</td>
<td>B</td>
<td>1 mo</td>
<td>2,410 990 1,090 17 7</td>
<td>NE 5.6</td>
<td>NE</td>
<td>+</td>
<td>-</td>
<td>Adenovirus</td>
</tr>
<tr>
<td>10</td>
<td>ND</td>
<td>4 mo</td>
<td>3,140 880 1,980 0-8 6-12</td>
<td>ND 2.5</td>
<td>ND</td>
<td>+</td>
<td>-</td>
<td>Enterovirus, RSV</td>
</tr>
<tr>
<td>11</td>
<td>A</td>
<td>20 mo</td>
<td>1,220 400 800 0 0</td>
<td>ND 1.56</td>
<td>NE</td>
<td>+</td>
<td>Eczema</td>
<td>Enterovirus, RSV, CMV</td>
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<tr>
<td>12</td>
<td>ND</td>
<td>8 mo</td>
<td>2,440 ND 1,290 1,400 0 0</td>
<td>ND 3.87</td>
<td>ND</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>A</td>
<td>4 yr</td>
<td>2,070 330 1,610 0 0</td>
<td>ND 18.7</td>
<td>NE</td>
<td>+</td>
<td>-</td>
<td>CMV</td>
</tr>
<tr>
<td>14</td>
<td>B</td>
<td>12 yr</td>
<td>2,450 1,720 290 0 0</td>
<td>ND 1.2</td>
<td>NE</td>
<td>+</td>
<td>-</td>
<td>Adenovirus</td>
</tr>
<tr>
<td>15</td>
<td>A</td>
<td>3 yr</td>
<td>2,140 750 1,460 0 0</td>
<td>ND 9.0</td>
<td>NE</td>
<td>+</td>
<td>Sepsis</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>B</td>
<td>22 mo</td>
<td>1,230 110 990 0 1</td>
<td>NE 8.2</td>
<td>NE</td>
<td>+</td>
<td>Sepsis, anal abscess</td>
<td>CMV, adenoVirus</td>
</tr>
<tr>
<td>17</td>
<td>B</td>
<td>5 mo</td>
<td>4,620 420 3,620 0 0</td>
<td>NE 6.7</td>
<td>NE</td>
<td>+</td>
<td>-</td>
<td>CMV</td>
</tr>
<tr>
<td>18</td>
<td>B</td>
<td>18 mo</td>
<td>2,280 940 1,060 0 0</td>
<td>NE 2.7</td>
<td>NE</td>
<td>+</td>
<td>-</td>
<td>Anal abscess</td>
</tr>
<tr>
<td>19</td>
<td>ND</td>
<td>6 mo</td>
<td>1,310 940 410 0 0</td>
<td>NE 2.9</td>
<td>NE</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

DR expression was evaluated on B cells (B), monocytes (M), and PHA-activated T cells (Tact). Normal values for lymphocyte subpopulations are age-dependent, roughly two age groups may be differentiated for CD3 counts: (1) <2 years, 3,000 to 9,000 cells/μL; (2) 2 to 12 years, 2,000 to 4,000 cells/μL. CD4 counts represent two-thirds and CD8 counts one-third of the CD3 counts. For exact reference values, see Erkelker-Yuksel et al.26

Abbreviations: NE, not evaluable due to previous Ig transfusion; ND, not done; Diss, dissociated.
<table>
<thead>
<tr>
<th>Patient No. (UPN)</th>
<th>Sex</th>
<th>Date of BMT (mo)</th>
<th>Age at BMT</th>
<th>HLA Identity</th>
<th>Conditioning Regimen</th>
<th>T-Cell Depletion Method</th>
<th>Nucleated Cells/kg ×10^6</th>
<th>Engraftment</th>
<th>GVHD</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (32)</td>
<td>M</td>
<td>4/81</td>
<td>18</td>
<td>6/6</td>
<td>1</td>
<td>6.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Death 13 mo post-BMT, CMV, enterovirus, pseudomonas sepsis</td>
</tr>
<tr>
<td>2 (43)</td>
<td>M</td>
<td>10/81</td>
<td>25</td>
<td>6/6</td>
<td>2</td>
<td>0.6</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Well, 11 yr post-BMT</td>
</tr>
<tr>
<td>3 (47)</td>
<td>F</td>
<td>4/83</td>
<td>65</td>
<td>6/6</td>
<td>3</td>
<td>1.5</td>
<td>+</td>
<td>+</td>
<td>II</td>
<td>Death 6 wk post-BMT, adenovirus infection</td>
</tr>
<tr>
<td>4 (81)</td>
<td>M</td>
<td>2/85</td>
<td>8</td>
<td>3/6</td>
<td>4</td>
<td>E-rosetting</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>Death 6 wk post-BMT, enterovirus, pneumonia</td>
</tr>
<tr>
<td>5 (82)</td>
<td>M</td>
<td>2/85</td>
<td>12</td>
<td>3/6</td>
<td>4</td>
<td>E-rosetting</td>
<td>0.9</td>
<td>–</td>
<td>–</td>
<td>Death 3 yr post-BMT, liver failure, sepsis</td>
</tr>
<tr>
<td>6 (84)</td>
<td>F</td>
<td>5/85</td>
<td>12</td>
<td>6/6</td>
<td>3</td>
<td>–</td>
<td>2.5</td>
<td>(+)</td>
<td>(+)</td>
<td>Death 8 wk post-BMT, CMV infection</td>
</tr>
<tr>
<td>7 (94)</td>
<td>M</td>
<td>11/85</td>
<td>74</td>
<td>3/6</td>
<td>5</td>
<td>E-rosetting</td>
<td>0.6</td>
<td>NE</td>
<td>NE</td>
<td>Death 3 wk post-BMT, overwhelming viral infection</td>
</tr>
<tr>
<td>8 (132)</td>
<td>F</td>
<td>4/87</td>
<td>28</td>
<td>3/6</td>
<td>5</td>
<td>E-rosetting</td>
<td>1.4</td>
<td>–</td>
<td>(+)</td>
<td>Alive 6.5 yr post-BMT</td>
</tr>
<tr>
<td>9 (143)</td>
<td>F</td>
<td>9/87</td>
<td>6</td>
<td>3/6</td>
<td>5</td>
<td>Campath 1M</td>
<td>5.5</td>
<td>–</td>
<td>–</td>
<td>Death 5 yr post-BMT, meningoencephalitis</td>
</tr>
<tr>
<td>10 (147)</td>
<td>M</td>
<td>11/7</td>
<td>7</td>
<td>5/6</td>
<td>5</td>
<td>–</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>Well 6 yr post-BMT</td>
</tr>
<tr>
<td>11 (152)</td>
<td>M</td>
<td>2/88</td>
<td>37</td>
<td>3/6</td>
<td>5</td>
<td>–</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>Death 3 mo post-BMT, CMV, adenovirus</td>
</tr>
<tr>
<td>12 (133ab)</td>
<td>M</td>
<td>4/87</td>
<td>11</td>
<td>3/6</td>
<td>5</td>
<td>E-rosetting</td>
<td>1.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>13 (252)</td>
<td>M</td>
<td>10/91</td>
<td>24</td>
<td>6/6</td>
<td>3</td>
<td>–</td>
<td>3.8</td>
<td>+</td>
<td>+</td>
<td>Well 5 yr post-BMT</td>
</tr>
<tr>
<td>14 (257)</td>
<td>F</td>
<td>11/91</td>
<td>18</td>
<td>3/6</td>
<td>6</td>
<td>E-rosetting</td>
<td>0.9</td>
<td>+</td>
<td>+</td>
<td>Well 3 yr post-BMT</td>
</tr>
<tr>
<td>15 (268)</td>
<td>M</td>
<td>4/92</td>
<td>65</td>
<td>3/6</td>
<td>6</td>
<td>E-rosetting</td>
<td>0.9</td>
<td>–</td>
<td>–</td>
<td>Persisting</td>
</tr>
<tr>
<td>16 (269)</td>
<td>M</td>
<td>5/92</td>
<td>117</td>
<td>3/6</td>
<td>6</td>
<td>Campath 1M</td>
<td>5.4</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7/92</td>
<td>119</td>
<td>3/6</td>
<td>6</td>
<td>Campath 1M</td>
<td>4.4</td>
<td>–</td>
<td>–</td>
<td>Death 2 mo post-BMT, CMV infection</td>
</tr>
<tr>
<td>17 (288)</td>
<td>F</td>
<td>2/92</td>
<td>17</td>
<td>6/6</td>
<td>3</td>
<td>–</td>
<td>4.8</td>
<td>+</td>
<td>+</td>
<td>Well 6 mo post-BMT</td>
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<tr>
<td>18 (287)</td>
<td>M</td>
<td>2/82</td>
<td>23</td>
<td>3/6</td>
<td>6</td>
<td>Campath 1M</td>
<td>5.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td></td>
<td>8/93</td>
<td>27</td>
<td>3/6</td>
<td>6</td>
<td>E-rosetting</td>
<td>0.7</td>
<td>(+)</td>
<td>–</td>
<td>–</td>
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<td>19 (296)</td>
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<td>5/93</td>
<td>9</td>
<td>3/6</td>
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<td>Campath 1M</td>
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<td>–</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>6/93</td>
<td>10</td>
<td>3/6</td>
<td>6</td>
<td>E-rosetting</td>
<td>0.5</td>
<td>+</td>
<td>+</td>
<td>–</td>
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HLA identity is based on HLA A, B, DR determination. Engraftment is based on DR expression on B cells and functional T-cell response and DR expression on PHA-activated T cells; (+) means evidence of partial engraftment.

Abbreviation: NE, not evaluable.

* Based on clinical suspicion.
deaths, as shown by viral culture of body fluids. All but the CMV infection of 2 recipients. All other patients with diarrhea, chorioretinitis, and psychomotor regression died of infection before BMT. In 4 cases, the viruses incriminated procedure (2 cases of CMV and 2 cases of enterovirus). Positive CMV cultures post-BMT had evidence of CMV infection within 1 year after BMT. All the patients had persistently low CD4+ cell counts, ranging from 105 to 650/µL at last follow up (Fig 1 and Table 3). This finding is consistent with impaired thymic maturation caused by defective HLA class II expression on thymic epithelia.

B-cell reconstitution. In the 7 patients with durable engraftment, B-cell counts returned to normal within a few weeks or months post-BMT. Ig levels normalized, with the exception of 1 patient who had reduced IgA levels and 2 patients with increased polyclonal IgM levels.

All 7 patients with durable engraftment had specific antibody production in response to immunization antigens (tetanus and diphtheria toxoids, poliovirus). None of the patients developed B-lymphoproliferative disorders.

Two patients (no. 2 and 10) have normal B-cell function despite chimerism (10% to 46% B cells of host origin).

Clinical course and infections. Seven patients died within 3 months after BMT of infectious complications. All of these early deaths were attributable to overwhelming viral infections leading to vital-organ failure, such as encephalitis and pneumonia, or lethal multiorgan involvement. CMV, enteroviruses, and adenovirus were responsible for the deaths, as shown by viral culture of body fluids. All but 3 patients (no. 7, 10, and 18) received grafts from CMV-seropositive donors, which may have been responsible for the CMV infection of 2 recipients. All other patients with positive CMV cultures post-BMT had evidence of CMV infection before BMT. In 4 cases, the viruses incriminated in lethal infections post-BMT had been identified before the procedure (2 cases of CMV and 2 cases of enterovirus). Three patients died more than 1 year post-BMT of infectious complications after graft failure. One patient (no. 1) who had chronic CMV and enterovirus infection leading to intractable diarrhea, chorioretinitis, and psychomotor regression died of Pseudomonas sepsis. Patient no. 5 developed Cryptosporidium-associated sclerosing cholangitis and liver failure and died of Pseudomonas sepsis. Patient no. 9 had recurrent bacterial and fungal infections, chronic enterovirus infection, pancreatitis, hepatitis, and oligoarthritis and died 5 years post-BMT of meningoencephalitis and cardiac arrest.

One patient (no. 8) with partial engraftment is momentarily stable 5 years post-BMT. One patient was rescued by autografting after two unsuccessful haploid BMT procedures. All the other patients are well, free of serious infections, and show normal physical and psychosocial development. One patient (no. 10) developed typical Kawasaki disease 3 years post-BMT that resolved without sequelae. At that time she was no longer receiving intravenous lgs. There was no correlation of favorable or unfavorable outcome with assignment to complementation groups.

Table 4. Immunologic Characteristics Post-BMT at Last Follow-Up

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Time Post-BMT</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CMV</th>
<th>BM</th>
<th>T-cell Stimulation (Ep)</th>
<th>Ig (µg/L)</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>13y</td>
<td>10 yr</td>
<td>2400</td>
<td>1900</td>
<td>480</td>
<td>890</td>
<td>2</td>
<td>G</td>
<td>A</td>
<td>10.8</td>
</tr>
<tr>
<td>8</td>
<td>9y</td>
<td>6 yr</td>
<td>2500</td>
<td>2200</td>
<td>400</td>
<td>900</td>
<td>2</td>
<td>G</td>
<td>A</td>
<td>10.8</td>
</tr>
<tr>
<td>10</td>
<td>6y</td>
<td>5 yr</td>
<td>3000</td>
<td>2700</td>
<td>500</td>
<td>1000</td>
<td>2</td>
<td>G</td>
<td>A</td>
<td>10.8</td>
</tr>
<tr>
<td>12</td>
<td>5y</td>
<td>4 yr</td>
<td>3500</td>
<td>3200</td>
<td>600</td>
<td>1200</td>
<td>2</td>
<td>G</td>
<td>A</td>
<td>10.8</td>
</tr>
<tr>
<td>13</td>
<td>4y</td>
<td>3 yr</td>
<td>4000</td>
<td>3700</td>
<td>700</td>
<td>1400</td>
<td>2</td>
<td>G</td>
<td>A</td>
<td>10.8</td>
</tr>
<tr>
<td>14</td>
<td>3y</td>
<td>2 yr</td>
<td>4500</td>
<td>4200</td>
<td>800</td>
<td>1600</td>
<td>2</td>
<td>G</td>
<td>A</td>
<td>10.8</td>
</tr>
<tr>
<td>15</td>
<td>2y</td>
<td>1 yr</td>
<td>5000</td>
<td>4700</td>
<td>900</td>
<td>1800</td>
<td>2</td>
<td>G</td>
<td>A</td>
<td>10.8</td>
</tr>
<tr>
<td>16</td>
<td>1y</td>
<td>6 mo</td>
<td>5500</td>
<td>5200</td>
<td>1000</td>
<td>2000</td>
<td>2</td>
<td>G</td>
<td>A</td>
<td>10.8</td>
</tr>
</tbody>
</table>

Abbreviation: N/A, not done.
Of 12 comparable children seen in our institution who did not undergo BMT, 5 died of overwhelming viral infections within the first 2 years of life and 1 died at age 16 of liver failure and gram-negative sepsis. The remaining 6 children (aged 2 to 16 years) have severe sequelae from recurrent infections and various autoimmune diseases.

**DISCUSSION**

BMT is now the treatment of choice for severe combined immunodeficiency disorders and has been shown to reconstitute the immune system in MHC class I deficiency (bare lymphocyte syndrome). However, preliminary analyses suggested that MHC class II-deficient patients did less well after BMT than other patients with combined immunodeficiencies. This finding is apparently borne out by our series of 19 patients, although no statistical analysis is possible. Four of seven children who underwent HLA-identical BMT were cured (the other 3 children died early, possibly due to inadequate conditioning and/or infection control). In contrast, only 3 of 12 children who underwent HLA-nonidentical BMT were cured, a rate lower than in other severe combined immunodeficiencies. One of the main obstacles to HLA-nonidentical BMT is infectious complications. Severe and persistent viral infections are a hallmark of MHC class II deficiency. Obviously, chronic viral carriage is a major danger in patients with BM ablation. Although the prognosis of HLA-nonidentical BMT has improved, mainly through better control of infections, the mortality rate among MHC-deficient patients, mainly due to overwhelming CMV, enterovirus, and adenovirus infections, remains high.

The main cause of treatment failure in HLA-nonidentical BMT is graft failure. This finding may be of particular importance in immunodeficiencies in which residual immune function inhibits engraftment, which include PNP-deficiency and combined immunodeficiency syndromes. In contrast to other forms of SCID, MHC class II-deficient patients develop a normal T-cell repertoire and show inducible alloreactive T lymphocytes that can initiate immunologic rejection or hamper engraftment. Over the last few years, significant improvements have been made in promoting engraftment. A protocol including anti-LFA-1 antibodies has been shown to facilitate engraftment. A subsequent protocol designed to further facilitate engraftment by addition of anti-CD2 antibodies is now being tested. In our study, the introduction of these protocols coincided with the development of full hematopoietic chimerism, without graft rejection, in successfully transplanted children, although engraftment failures still occurred. Other factors, such as the detrimental influence of viral infections, may play a role in engraftment failure.

Age at the time of transplantation has been identified as a risk factor in BMT for immunodeficiencies. Patients less than 2 years of age do better than older patients. This difference seems to be especially true of MHC class II-deficient patients, because only one child underwent successful HLA-identical BMT (no cases of successful haploidentical BMT) after 24 months of age. The kinetics of immune reconstitution after BMT did not differ from that in other primary immunodeficiency conditions.

Before BMT, patients with MHC class II deficiency showed low CD4+ cell counts, with a compensatory increase in CD8+ lymphocytes. This combination is reminiscent of MHC class II-knockout mice. However, in contrast to MHC class II-deficient mice, the proportion of CD4+ lymphocytes was higher in the patients, possibly due to residual HLA class II expression in the thymus. Interestingly, low CD4+ cell counts persisted after BMT, possibly reflecting...
impaired thymic maturation of CD4+ cells due to decreased
MHC class II expression in the thymic epithelium. This also
provides indirect evidence that donor BM-derived cells are
not critical for positive thymic selection of CD4+ T cells.33

Clinically, CD4 lymphopenia was not associated with in-
creased susceptibility to infections. In addition, despite a
lack of MHC class II reconstitution in nonhematopoietic
cells, infection control does occur. The antigen-presenting
function of activated endothelial and epithelial cells therefore
seems to be dispensable when BM-derived antigen-pre-
senting cells are functional.

Further studies to identify molecular defects are under-
way. There is some hope that, as in other primary immunode-
ficiency disorders,34 gene therapy might improve the cure
rate in MHC class II deficiency in the future. Given the
dismal prognosis of patients with MHC class II deficiency,
BMT is, in our opinion, the treatment of choice today, pro-
vided it is performed early in life, before the onset of infec-
tion-related complications.

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