CORRESPONDENCE

Cyclophosphamide Plus ATG Conditioning Is Insufficient for Sustained Hematopoietic Reconstitution in Patients With Severe Aplastic Anemia Transplanted With Marrow From HLA-A, B, DRB Matched Unrelated Donors

To the Editor:

We have recently described the use of a cyclophosphamide (Cy; 50 mg/kg/d X 4) plus antithymocyte globulin (ATG; 30 mg/kg/d X 3) conditioning regimen in patients with severe aplastic anemia (SAA) given a marrow transplant from an HLA-genotypically or phenotypically identical related donor: 32/33 patients achieved sustained engraftment and 30 (91%) are surviving 12 to 66 (median 38) months after transplant.1 We now applied the same Cy/ATG regimen to 5 patients with SAA transplanted with marrow from phenotypically matched unrelated donors under the hypothesis that the approach would be as successful as with related donors. All patients were multiply transfused, two were platelet transfusion refractory, and all had received multiple courses of immunosuppressive therapy (Table 1). Donor/recipient pairs were identical for HLA class I and class II antigens by serologic typing and for DRB, at the molecular level as determined by sequence specific oligonucleotide probes.2 All patients received methotrexate plus cyclosporine as graft versus host disease (GVHD) prophylaxis.3 Methods of documentation of hematopoietic engraftment, the management of GVHD and other supportive care have been described elsewhere.4,5

Data are summarized in Table 1. One patient with a 12-year history of SAA died on day 3 from intracranial hemorrhage and was not evaluable for engraftment. One patient achieved engraftment, but died on day 22 with GVHD and veno-occlusive disease of the liver. Among the three patients surviving beyond 1 month, none achieved a well-functioning graft. One of these patients rejected the graft and is alive at 403 days with severe marrow aplasia. Two patients remained pancytopenic with persisting donor cell engraftment and required continued red blood cell and platelet transfusion support; one died on day 166 with septicemia, and one is alive on day 124 receiving treatment with granulocyte-colony stimulating factor. Therefore, it appears that the present regimen cannot be recommended as a standard approach in patients transplanted from an unrelated donor.

The causes of these poor results are probably multiple6-8: (1) All patients had received multiple cycles of immunosuppressive therapy. Whereas immunosuppressive therapy had also been given to about half of the patients transplanted from a related donor, the time interval from diagnosis was far longer among unrelated (median 41 months) than among related recipients (median 2.5 months) and transfusion support had been extensive in all. (2) Histocompatibility differences other than HLA-A, B and DR may represent a barrier not overcome by Cy plus ATG. An increased probability of graft failure was observed in a larger study of patients with leukemia even among patients transplanted from phenotypically HLA-matched related donors.9 The difference in non-HLA antigens may be even larger between unrelated individuals. (3) Marrow microenvironmental defects may have contributed to graft failure. This appears to be an infrequent problem in patients given grafts from a related donor and after unrelated transplants in patients with leukemia conditioned with more aggressive regimens. However, it is conceivable that in comparison to patients with leukemia, a Cy/ATG regimen in patients with SAA was insufficient for conditioning the microenvironment such that donor cells were optimally supported.

Although the number of patients in the present study was small, results were discouraging. At the present time, alternative modalities of conditioning, including irradiation may be preferable. As new agents become available, eg, appropriate monoclonal antibodies with or without toxin or radioisotope conjugation, more effective preparative regimens can be designed.

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Table 1. Patient Characteristics and Transplant Outcome

<table>
<thead>
<tr>
<th>Patient No. (UPN)</th>
<th>Interval to BMT (mos)</th>
<th>Previous Therapy</th>
<th>Patient Age (yrs)</th>
<th>Donor Sex/ Patient Sex</th>
<th>Engraftment</th>
<th>Acute GVHD (grade)</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>6463</td>
<td>144</td>
<td>AND, PDN, Cy, CSP</td>
<td>19</td>
<td>M/F</td>
<td>NE</td>
<td>NE</td>
<td>Died, d 3, intracranial hemorrhage</td>
</tr>
<tr>
<td>6822</td>
<td>18</td>
<td>AND, ATG, CSP</td>
<td>17</td>
<td>F/M</td>
<td>No</td>
<td>No</td>
<td>Alive &gt; d 403, marrow aplasia</td>
</tr>
<tr>
<td>7172</td>
<td>141</td>
<td>ATG, CSP, PDN</td>
<td>21</td>
<td>M/M</td>
<td>Yes</td>
<td>Yes (III)</td>
<td>Died, d 166, septicemia; poor graft function</td>
</tr>
<tr>
<td>7225</td>
<td>41</td>
<td>PDN, ATG, CSP X2, DAN, GM-CSF, EPO</td>
<td>23</td>
<td>M/F</td>
<td>Yes (III)</td>
<td>Died, d 22, veno-occlusive disease of the liver</td>
<td></td>
</tr>
<tr>
<td>7663</td>
<td>22</td>
<td>ATG, PDN, CSP X2</td>
<td>18</td>
<td>M/F</td>
<td>No</td>
<td>No</td>
<td>Alive &gt; d 124, pancytopenia, severe marrow hypoplasia</td>
</tr>
</tbody>
</table>

Abbreviation: UPN, unique patient number; NE, not evaluable; AND, androgens; PDN, glucocorticoids; CSP, cyclosporine; DAN, danazole; GM-CSF, granulocyte-macrophage colony-stimulating factor; EPO, erythropoietin.

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REFERENCES


Cyclophosphamide plus ATG conditioning is insufficient for sustained hematopoietic reconstitution in patients with severe aplastic anemia transplanted with marrow from HLA-A, B, DRB matched unrelated donors [letter]

HJ Deeg, C Anasetti, E Petersdorf, R Storb, K Doney, JA Hansen, J Sanders, KM Sullivan and FR Appelbaum