Granulocyte Colony-Stimulating Factor-Mobilized Allogeneic Peripheral Blood Stem Cells for Rescue Graft Failure After Allogeneic Bone Marrow Transplantation in Two Patients With Acute Myeloblastic Leukemia in First Complete Remission

To the Editor:

Although engraftment is the rule after allogeneic unmanipulated HLA-matched bone marrow transplantation (BMT), some patients fail to engraft and others develop secondary graft failure. Despite the use of human recombinant colony-stimulating factors (CSFs), supportive care, or reimplantation of second marrow transplant, mortality after graft failure remains high. In autologous transplantation, the addition of granulocyte-CSF (G-CSF)-mobilized peripheral blood mononuclear cells (PBMCs) improves hematopoietic recovery, and the same could be assumed in an allogeneic situation. We report here two cases of allogeneic graft failure who successfully recovered hematopoiesis after the use of allogeneic G-CSF-mobilized peripheral blood stem cells without additional conditioning and without CSF administration after PBMC infusion.

Two patients, a 38-year-old man (patient A) and a 29-year-old man (patient B), underwent allogeneic BMT from an HLA-identical sibling for acute myeloblastic leukemia (respectively, M1 and M2) in first remission. The conditioning regimen consisted of 120 mg/kg cyclophosphamide and 12 Gy fractioned total body irradiation. They received, respectively, 16.2 $\times$ 10^5 colony-forming units-granulocyte-macrophage (CFU-GM)/kg and 7.8 $\times$ 10^4 CFU-GM/kg. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin (CsA) and short methotrexate. At day +28, both patients had white blood cell (WBC) counts at 0.1 g/L, with no neutrophils. An infectious process (particularly a cytomegalovirus [CMV] infection), relapse, and other causes of graft failure were ruled out. Both patients were treated with G-CSF at 5 $\mu$g/kg/d for 14 days, without any result.

Patient A received a second BMT at day +50 from another HLA-identical sibling, with antithymocyte globulin as conditioning. During week 2 post-second BMT, the WBC count reached 0.9 g/L, with 0.7 g/L neutrophils, but 1 week later, the absolute neutrophil count (ANC) was less than 0.1 $\times$ 10^9/L. G-CSF was reinitiated without improvement of ANC. Typing of residual cells was performed with DNA restriction fragment length polymorphism (RFLP) analysis, and only cells from the second donor were present. In light of this result, we decided to perform a third transplant with G-CSF-mobilized PBMCs from the second donor without conditioning regimen. For patient B, residual cells were typed with RFLP, again showing the presence of residual donor cells, and the decision was the same.

After signed informed consent was obtained, the donors received G-CSF (Roche, Paris, France) at 16 $\mu$g/kg/d for 5 consecutive days by a subcutaneous injection without any side effects. Leukapheresis was performed from day +4 to day +6 for the first donor and from day +4 to day +7 for the second donor; both were well tolerated. Collection characteristics are shown in Table 1.

Patient A received the first infusion of PBMCs at day +97 of his first graft (and at day +47 of his second graft). For patient B, it was at day +69 of his BMT.

For both patients, PBMCs were infused without ex vivo manipulation. Posttransplant growth factors were not administered. Day 0 was the day of the first PBMC infusion. No GVHD prophylaxis was administered.

For patient A, the ANC reached 0.5 and 1.0 $\times$ 10^9/L at day +14 and day +19, respectively; the patient became platelet transfusion independent at day +25. He presented a CMV gastrointestinal disease at day +62 of his PBMC graft and was successfully treated by gancyclovir and high-dose intravenous Igs. Graft function was not affected during this episode. The patient is currently well at a follow-up of 324 days, with no GVHD or graft failure and a complete donor's chimerism.

For patient B, ANC reached 0.5 and 1.0 $\times$ 10^9/L at day +14 and day +15, respectively; he became platelet transfusion independent at day +36. No acute GVHD occurred. Subsequently, he presented several infectious complications, particularly a CMV gastrointestinal

<table>
<thead>
<tr>
<th>Patient</th>
<th>TMC ($\times$ 10^6/kg)</th>
<th>CFU-GM ($\times$ 10^5/kg)</th>
<th>CD34+ ($\times$ 10^6/kg)</th>
<th>CD3 Cells ($\times$ 10^6/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient A</td>
<td>18.2</td>
<td>10.6</td>
<td>25.2</td>
<td>7.56</td>
</tr>
<tr>
<td>Patient B</td>
<td>16.9</td>
<td>1.08</td>
<td>46.3</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Abbreviation: TMC, total mononuclear cells.
disease (without gross effect on WBC count) at day +43 of his transplantation. Prognosis after graft failure is very poor. In these two cases, graft failure has been overcome by infusion of G-CSF-mobilized PBMCs. Both patients failed to engraft with bone marrow and successfully recovered hematopoiesis after PBMC infusion. Possible causes of graft failure were carefully searched and ruled out, particularly CMV infection, before PBMC infusion. Furthermore, the increase of the ANC occurred, as typically expected, after PBMC infusion, without the addition of CSF. The use of a high number of CD34+ cells and/or CFU-GM may have been an important factor for successful engraftment in these cases. The number of transplanted cells has been shown to be important in mice for engraftment; the same is assumed in humans. The quantity and/or the quality of T lymphocytes may be an other important factor. In humans, the extensive clinical trials with T-cell depletion in the 1980s led to a recognition of the importance of T cells in engraftment and in GVHD. The number of CD3+ lymphocytes in PBMC collection was approximately 1 log more than the number of T lymphocytes collected in bone marrow harvest. In our two patients, the presence of more T lymphocytes may have facilitated hematopoiesis recovery through the production of cytokines that promote the growth and the differentiation of hematopoietic stem cells or through other unknown mechanisms. In regards to GVHD, none of our patients had a GVHD prophylaxis or then developed acute GVHD, suggesting that the quality (ie, specificity) rather than the quantity of donor T cells may be an important determinant for GVHD development and that allogeneic PBMC transplantation is feasible without causing detrimental GVHD.

The use of PBMCs will probably increase in allogeneic transplantation. Prognosis after graft failure is very poor. If chimerism is proved, a conditioning regimen may be unnecessary, thus decreasing toxicity. In these two observations, G-CSF-mobilized PBMCs have been more efficient for hematopoietic recovery than marrow graft, but the reasons for this are unclear. This type of procedure offers an interesting alternative. The safe collection of allogeneic PBMCs in healthy donors can be useful at least for the treatment of engraftment failure.

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REFERENCES


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