Mixed Chimerism After Bone Marrow Transplantation and the Risk of Relapse

To the Editor:

After bone marrow transplantation, recipient hematopoietic cells are usually eradicated by the combination of the cytotoxic preconditioning regimen and the allogeic effect of the mature T cells in the graft. Whenever one of these effects is weakened, recipient cells might persist. Therefore, recipient cells can be detected either when a less cytotoxic preconditioning regimen is used, so that the patient's marrow can survive, when a standard preconditioning regimen exerts its cytotoxic effects less efficiently in very young children, or when a patient is grafted with a T-cell-depleted marrow. In the latter case, the presence of recipient cells reflects a state of tolerance of the transferred donor immune system versus the host, and therefore a correlation will be found between the persistence of recipient cells, ie, mixed chimerism (MC) and the absence of graft-versus-host disease (GVHD). Because this state of tolerance might also facilitate the survival of the malignant clone, one could assume that the evolution of MC would be able to predict a forthcoming relapse. However, observations on the correlation of the occurrence of MC and an increased risk of relapse have not been concordant, and two reports recently published in Blood come to an apparent contradictory conclusion. Whereas van Leeuwen et al showed that the persistence of MC after marrow transplantation for leukemia was not associated with an increased risk of recurrent disease, Mackinnon et al reported a good correlation between the occurrence of MC and minimal residual disease with subsequent relapse. However, this discrepancy might be explained by considering the different types of leukemia's reported on and their respective sensitivity to the graft-versus-leukemia effect (GVL). Obviously, a graft-versus-host tolerance will have more consequences for a leukemia for which low relapse rates are primarily dependent on GVL. Chronic myeloid leukemia (CML) is the best example of such a leukemia, as is clearly indicated by the fact that relapse rates increase significantly when the donor is a monozygous twin and by the fact that, in contrast to other types of leukemias, relapses after bone marrow transplantation can be treated successfully by donor lymphocyte infusions. Therefore, MC being the hallmark of a state of tolerance will be more significantly correlated with an increased risk of relapse for CML than for acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). The results (Table 1) in our patient group (N = 48) illustrate this point. Whereas for all patients MC and the absence of GVHD were rigorously correlated with the induction of tolerance in the graft by the Campath-1M T-cell depletion, this state of tolerance did increase the number of relapses in CML patients only. Whether a correlation between the occurrence of MC and an increased risk for relapse will be found would therefore depend on the percentage of the CML patients in the group studied. Because this "CML-effect" is present in most studies published, this could perfectly explain the apparent contradictory conclusions drawn by the different investigators.

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Table 1. Relapse in Patients With MC or Complete Chimerism

<table>
<thead>
<tr>
<th>MC (32)</th>
<th>CC (16)</th>
<th>CML</th>
<th>MC (8)</th>
<th>CC (8)</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>GVHD ≥2</td>
<td>0 (0%)</td>
<td>12 (75%)</td>
<td>MC (8)</td>
<td>CC (8)</td>
<td>MC (6)</td>
</tr>
<tr>
<td>Relapse</td>
<td>11 (31%)</td>
<td>2 (12%)</td>
<td>7 (87%)</td>
<td>0 (0%)</td>
<td>1 (17%)</td>
</tr>
</tbody>
</table>

Abbreviation: CC, complete chimerism.

* Disease: AML, N = 18; CML, N = 16; ALL, N = 14. AML patients are not depicted in detail because this group, having all received a T-cell-depleted graft, is not informative.

† Thirty-two of 33 patients who had received a T-cell-depleted graft were MCs, whereas no recipient cells were detected in the patients who received unmanipulated grafts.
REFERENCES


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