selected allogeneic stem cell transplantation was observed. Patients receiving bone marrow from unrelated donors followed by an intensified GVHD prophylaxis showed CMV PCR positivity even sooner after transplantation, but again PCR-based antiviral therapy was found to be safe with only 1 patient developing early fatal CMV disease as already reported previously.2 But this group seemed to be at an increased risk for late onset CMV disease most likely due to a delayed reconstitution of CMV-specific T-cell responses.3,4

In conclusion, as discussed by Holmberg et al and demonstrated in this study, the high incidence of CMV disease in recipients of CD34-selected stem cells can be reduced by the early initiation of preemptive antiviral therapy based on sensitive assays,1,6 but probably to the expense of an increased incidence of late-onset CMV disease, especially in patients with delayed immune reconstitution.7,9

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Table 2. Reconstitution of T-cell subpopulations at 3 and 6 months after transplantation

<table>
<thead>
<tr>
<th>Group I: unselected PBPCs</th>
<th>Group II: CD34+ selected PBPCs</th>
<th>Group III: BMT from an unrelated donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 3 months (n = 10)</td>
<td>(n = 10)</td>
<td>(n = 13)</td>
</tr>
<tr>
<td>CD3+ T cells</td>
<td>434; 111-803</td>
<td>842; 128-2875</td>
</tr>
<tr>
<td>CD4+ T cells</td>
<td>75; 46-146</td>
<td>186; 42-350</td>
</tr>
<tr>
<td>CD8+ T cells</td>
<td>308; 38-628</td>
<td>622; 57-2531</td>
</tr>
<tr>
<td>At 6 months (n = 9)</td>
<td>(n = 7)</td>
<td>(n = 8)</td>
</tr>
<tr>
<td>CD3+ T cells</td>
<td>586; 164-2090</td>
<td>724; 177-2728</td>
</tr>
<tr>
<td>CD4+ T cells</td>
<td>110; 45-625</td>
<td>147; 51-263</td>
</tr>
<tr>
<td>CD8+ T cells</td>
<td>455; 50-1650</td>
<td>535; 78-2334</td>
</tr>
</tbody>
</table>

Each entry is median number of T cells per microliter; range.

PBPCs, peripheral blood progenitor cell transplants; BMT, bone marrow transplantation.

References

leukemic transformation. Second, despite the high incidence of ELA2 mutations in cyclic neutropenia, 2 of which (16073G>A and 15862C>T) are also found in CN, none of the 132 cyclic neutropenia patients reported so far developed leukemia. How the ELA2 mutations contribute to the pathogenesis of neutropenia remains unclear until the biological properties of the various mutated neutrophil elastase proteins have been elucidated. But there is no indication that ELA2 mutations are involved in leukemic progression of CN.

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References

Response:

Neutrophil elastase and congenital neutropenia

Drs Hermans and Touw have questioned the suggestion in our paper that mutations of the gene for neutrophil elastase create the risk for leukemia in patients with congenital neutropenia. We made this hypothesis based on the following:

1. Most patients with severe congenital neutropenia have mutations of the gene for neutrophil elastase (ELA2). At the recent meeting of the American Society of Hematology, we reported the information in our paper and reported that 45 of 49 patients examined have mutations of the ELA2 gene. Thus this mutation is far more common than mutations of the G-CSF receptor gene (G-CSF-R).1

2. Our report indicates that families with autosomal dominant congenital neutropenia have the same mutation in all family members. This demonstrates that these are germline mutations and not acquired mutations. Thus far, all evidence points to the G-CSF-R mutations as being acquired mutations.2

3. We have now serially studied one patient with congenital neutropenia, having a mutation of the ELA-2 gene, who then developed leukemia. Prior to the development of leukemia, the G-CSF-R was normal, but the ELA-2 gene was abnormal. The G-CSF-R became abnormal when he developed leukemia.3

4. In our Seattle studies of patients with severe congenital neutropenia evolving to leukemia, 6 of 7 patients have had ELA2 mutations. Five of the 6 with ELA2 gene mutations evolving to leukemia have had G-CSF-R mutations.

5. In cellular studies, we have found that patients with congenital neutropenia and mutations of the ELA2 gene have accelerated apoptosis of CD34+ precursor cells. In patients evolving to leukemia and having G-CSF-R mutations, we have found that the cells manifest longer survival. It may be inferred that cells bearing the mutant receptor accumulate as part of the leukemic transformation.

Based on these data, we agree with Drs Hermans and Touw that G-CSF-R mutations are common in patients with congenital neutropenia who develop leukemia. Thus far, the data is compelling in indicating that the mutations in the gene for ELA2 come first.

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References

To the editor:

Drug-dependent antibodies against the prodrug carbimazole do not react with the active metabolite thiamazole

Drug-induced immune thrombocytopenia (DITP) is a sometimes severe complication of drug treatment. Recently, we described 5 patients who presented with relatively mild thrombocytopenia after treatment with the antithyroid drug carbimazole (1-carbethoxy-3-methyl-2-thioimidazole).1 Serologic and immunochemical analysis revealed drug-dependent antibodies (DDAbs) against the platelet
Significance of neutrophil elastase mutations versus G-CSF receptor mutations for leukemic progression of congenital neutropenia

Mirjam H. A. Hermans and Ivo P. Touw