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 updated 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
endothelial cell adhesion molecule-1 (PECAM-1, CD31). Because the chemical analog of carbimazole, thiamazole (3-methyl-2-thioimidazole), is widely used for the treatment of hyperthyroidism in the US, we asked the question whether carbimazole DDAbs cross-reacted with thiamazole. Sera from 4 patients of our initial study (patients 2-5; patient 1 died and no further serum was available) were analyzed by enzyme immunoassay with intact platelets in the presence and in the absence of 1 mg/mL carbimazole or thiamazole, as previously described. As shown in Figure 1, all carbimazole DDAbs failed to react with platelets in the presence of thiamazole. Analysis of DDAbs in the glycoprotein-specific immunoassay (MAIPA) revealed positive reactions with PECAM-1 in the presence of carbimazole but not with thiamazole (data not shown). Specific interaction between carbimazole and the platelet membrane has to be assumed because only a minor chemical modification of carbimazole led to destruction of the carbimazole DDAb reactivity. This has already been suggested by our finding that the second extracellular loop of PECAM-1 was crucial for epitope formation. In addition, the carbethoxy group of carbimazole at position C-1 seems to be important for the immune response and subsequent thrombocytopenia in the patient after drug treatment. Carbimazole is a prodrug that is rapidly and totally converted to thiamazole in the body by cleavage of the carbethoxy group. This phenomenon could contribute to the clinical presentation of mild thrombocytopenia in our patients. Due to the high specificity of DDAbs, binding and platelet destruction could only occur during the phase immediately after carbimazole administration. After metabolism to thiamazole, no further platelet destruction takes place. This phenomenon might represent an interesting counterpart of the situation observed in patients in whom metabolite-specific DDAbs induce a prolonged effect in relation to drug excretion. We conclude that both the chemical structure and the metabolism of the drug may have a major influence on the clinical presentation of DITP, particularly on the degree of thrombocytopenia. Further observations will be required to define whether thiamazole itself is able to raise a drug-dependent immune response against platelets.

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References
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