Methemoglobinemia Secondary to Clofazimine Treatment for Chronic Graft-Versus-Host Disease

To the Editor:

Chronic graft-versus-host disease (cGVHD) is a frequent late complication of allogeneic bone marrow transplantation (allo-BMT), affecting 20% to 50% of long-term transplant survivors. A wide combination of agents have been used as primary therapy for extensive cGVHD, but none has proved to be completely effective against extensive multiorgan involvement. Meanwhile, because conventional agents have been associated with significant therapy-related complications, several alternative approaches have been reported in the treatment of cGVHD. Lee et al have recently reported their successful experience with clofazimine as treatment to skin involvement, flexion contractures, or oral manifestations for patients with cGVHD. Mild gastrointestinal side effects and red-brown hyperpigmentation of the skin and conjunctiva were the only complications noted. We report a case of acquired methemoglobinemia (metHb) secondary to clofazimine treatment for cGVHD after allo-BMT.

An 8-year-old girl with severe aplastic anemia received an HLA-identical allo-BMT prepared with busulphan and cyclophosphamide. GVHD prophylaxis was cyclosporine (CSA) and methotrexate. She developed an extensive progressive cGVHD, which included lichenoid involvement. Meanwhile, because conventional agents have been used as primary therapy for extensive cGVHD, affecting 20% to 50% of long-term transplant survivors.1 A wide combination of agents have been used as primary therapy for extensive cGVHD, affecting 20% to 50% of long-term transplant survivors.2,3 but none has proved to be completely effective against extensive multiorgan involvement.2,3 Meanwhile, because conventional agents have been associated with significant therapy-related complications, several alternative approaches have been reported in the treatment of cGVHD.4,5 Lee et al have recently reported their successful experience with clofazimine as treatment to skin involvement, flexion contractures, or oral manifestations for patients with cGVHD. Mild gastrointestinal side effects and red-brown hyperpigmentation of the skin and conjunctiva were the only complications noted.6 We report a case of acquired methemoglobinemia (metHb) secondary to clofazimine treatment for cGVHD after allo-BMT.

Methemoglobin results from oxidation of the iron moieties in hemoglobin from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state and becomes incapable of binding and transporting oxygen. A diagnosis of MetHb is made when more than 1% of hemoglobin exists in the oxidized (Fe^{3+}) form. The condition may be congenital or acquired, and several drugs and chemicals have been reported to induce methHb. Therefore, exogenous electron carriers, such as methylene blue, can serve as pharmacologic agents for the treatment of metHb.

Clofazimine’s chemical structure is 3-(p-chloroanilino)-10-[(p-chlorophenyl)-2,10-dihydro-2-isopropyliminophenazine. Despite reports describing otherwise, the clofazimine molecule contains two radicals reported to mediate iron hemoglobin oxidation. The first molecule is 3-p-chloroanilino (aniline dye), a para-aminophenol derivative with low anti-inflammatory actions, long known for its hemoglobin-oxidating capacities.7 The second radical, isopropyliminophenazine, a pyrazolon derivative, has also had its hemoglobin iron oxidation properties extensively reported in the literature, especially under hypoxic conditions.8 Its mechanism of action seems to be related to the reduction of glutathione peroxidase and catalase, originating methemoglobin.9 To the best of our knowledge, this is the first report of methHb secondary to clofazimine therapy.

Because clofazimine is a new drug in this setting, with a potentially broader utilization as first-line treatment due to its encouraging efficacy and lack of infectious complications, physicians must be aware of this rare and reversible, but potentially dangerous adverse reaction.

Vanezura de A. Moreira
Bruno C. De Medeiros
Carmen M.S. Bonfim
Ricardo Pasquini
Carlos R. De Medeiros
Serviço de Transplante de Medula Òssea
Hospital de Clínicas
UFPR
Curitiba, Brazil

REFERENCES


Bone Marrow Transplantation, Fetal B-Cell Repertoire Development, and the Mechanism of Immune Reconstitution

To the Editor:

Studies of bone marrow (or stem cell) transplantation (BMT) provide important insights in immunological and genetic mechanisms that form the human immune system. Guillaume et al. published an excellent review of postransplant B- and T-cell repertoires in the context of therapeutic strategies that could enhance the outcome of BMT. However, they suggested that immune reconstitution after BMT follows a fetal program of development, and I think this warrants further discussion.

The early post-BMT B-cell repertoire is usually characterized as fetal because it appears to be dominated by VH elements that are frequently detected in fetal liver (most particularly VH6). Formation of the human fetal VH repertoire has long been thought to be guided by the location of the VH elements, with JH-proximal VH segments (such as VH6) rearranging most frequently. However, current evidence contradicts this mechanism. For instance, analysis of VH6 expression in fetal tissue with a monoclonal antibody failed to support increased VH6 levels as determined by random sequencing and Northern blot analysis. Overexpression of the VH6 element can therefore no longer be regarded as a characteristic of the fetal repertoire. In addition, because the B-cell repertoire is dominated by (oligo)clonal expansions early after BMT, measurement of VH family expression levels may not be the most suitable marker to distinguish fetal- or adult-type immune reconstitution. It is possible that patterns of VH expression determined by Northern blotting, random sequencing, or VH family-specific polymerase chain reaction are skewed by dominant clones that express particular VH families.

What then defines a fetal repertoire? Fetal antigen receptors characteristically contain antigen-binding pockets that are encoded by relatively short third complementarity-determining regions (CDR3). The importance of this characteristic is reflected by the fact that it is conserved through evolution— it has been detected in species as diverse as frogs, rabbits, mice, and humans and holds true for both B- and T-cell receptors. Prime determinants of CDR3 size are the usage pattern of diversity (DH) elements and the length and frequency of N-regions—stretches of DNA that are added by the enzyme terminal deoxynucleotidyl transferase during formation of the antigen receptor gene. As compared with the situation in the adult, N-regions are expressed at lower frequencies during fetal development. For instance, an estimated 20% of CDR3 regions in 12- to 14-week-old fetal livers lack N-regions altogether. In addition, up to 50% of fetal B-cell receptor CDR3 segments use the DQ52 DH element (which is relatively small).

By contrast to this fetal pattern of CDR3 diversity, CDR3 regions in adult peripheral blood are longer and more diverse; they rarely express DQ52, and they contain extensive addition of N-regions in all instances. Given the clear difference between fetal- and adult-type antigen receptors, the pattern of CDR3 diversity is a more reliable marker for distinction between fetal and adult repertoires.

To date, studies of the post-BMT repertoire demonstrated that CDR3 regions of reconstituting B cells exhibit none of the characteristics that define a fetal repertoire: they rarely encode DQ52, they exhibit adult patterns of N-region addition, and their general size is indistinguishable from that in adult peripheral blood. This pattern of diversity is identical to that in adult bone marrow pre-B cells (which also produce adult-type CDR3 regions). In other words, there is no reason to expect a recapitulation of fetal development after BMT, because the graft, consisting of adult lymphoid progenitors, is placed in the adult environment of the recipient.

In conclusion, immune reconstitution after BMT follows many established ontogenetic patterns relating to the appearance of particular membrane markers, Ig subclasses, and onset of antigen receptor rearrangements. The sequence of events that occur during successful BMT can be regarded as a blueprint for immune reconstitution in other clinical settings as well. However, in the description and interpretation of these events, it is important to realize that immune reconstitution does not appear to recapitulate human fetal ontogeny.

F.M. Raaphorst
Department of Pathology
VU Academic Hospital
Amsterdam, The Netherlands

REFERENCES
Methemoglobinemia Secondary to Clofazimine Treatment for Chronic Graft-Versus-Host Disease

Vaneuza de A. Moreira, Bruno C. De Medeiros, Carmen M.S. Bonfim, Ricardo Pasquini and Carlos R. De Medeiros

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