blood® Editorial

Introduction to a How I Treat series on sickle cell disease and thalassemia

An estimated 7% of the world's population carries a mutation for a monogenetic disorder of hemoglobin, resulting in >250 000 individuals born each year with clinically significant sickle cell disease and >300 000 born each year with thalassemia. The outlook for both disorders has improved substantially for patients with access to modern medical care. The median survival in the United States for sickle cell disease was ~12 to 15 years in the 1970s. With the advent of penicillin prophylaxis, pneumococcal vaccine, hydroxyurea, and stroke screening, >95% of individuals are alive at age 18 years, and overall median survival has recently been estimated to be in the late 50s and even the mid-to-late 60s in countries with organized access to health care. Nevertheless, although survival has greatly improved, morbidity remains significant for this population. An estimated 240 000 children are born with sickle cell disease each year in Africa, with only a small percentage surviving past 2 years of age. However, concerted efforts by a number of groups to introduce newborn screening, penicillin, and, importantly, hydroxyurea in African countries with the highest density of sickle cell disease patients show great promise. Similarly, the median survival for thalassemia major was 3 to 4 years in the 1950s; it increased to 15 years of age in the 1960s with the implementation of regular blood transfusions. The cause of death then shifted to transfusion-related iron overload. The introduction of effective parenteral chelation in the early 1970s, and later of oral chelators and magnetic resonance imaging monitoring of cardiac and total iron, has reduced complications due to iron overload, and deaths from iron cardiomyopathy dropped dramatically in regions of the world with access to modern medicine. We now know that cardiomyopathy can almost always be reversed, although improvement in the endocrinological and malignant consequences is not so certain.

With the marked improvement in survival, these disorders, which were once primarily the domain of the pediatrician, are now increasingly presenting to the internal medicine physician and even the geriatrician. As a consequence of the longer survival, patients are now at risk for complications associated with their long-term chronic illness, in addition to those due to aging. Thus, the longer survival forces us to rethink our treatment of the young. For example, control of iron overload initially focused on keeping patients from dying of heart failure in their second and third decade, and deaths have dramatically decreased. However, epidemiological data show that the risk of leukemia and lymphoma in transfused thalassemia patients past their fourth decade is ninefold that of nontransfused patients and is significantly higher than in the general population, unmasking new complications related to decades of exposure to iron. Therefore, levels of iron control that prevent heart failure may not be sufficient to reduce the propensity for malignant transformation. The longer survival poses additional issues for these patients related to special expertise in the adult world. There are few centers with significant experience and a focus on hemoglobin disorders in adults, or children for that matter. Such special expertise can greatly affect survival and morbidity.

In this issue of *Blood*, we present a series of invited reviews that discuss the problems faced by hemoglobinopathy patients who have survived into adulthood. The reviews in this series include the following:

- Swee Lay Thein and Jo Howard, "How I treat the older adult with sickle cell disease"
- Arun S. Shet and Ted Wun, "How I diagnose and treat venous thromboembolism in sickle cell disease"
- Evans M. Machogu and Roberto F. Machado, "How I treat hypoxia in adults with hemoglobinopathies and hemolytic disorders"
- Ali T. Taher and Maria Domenica Cappellini, "How I manage medical complications of β-thalassemia in adults"

Thein and Howard address the complications of older sickle cell patients and the importance of maintaining hemoglobin levels and preventing organ damage. They recommend a focus on curative treatments in the young before complications occur.

Shet and Wun address the important topic of venous thromboembolism in sickle cell disease and point out that sickle cell disease is, in fact, a hypercoagulable state. This is an excellent example of the natural increase in thrombosis with age interacting with a disease that predisposes to clotting.

Machogu and Machado discuss the pulmonary consequence of hemoglobinopathy and chronic hemolysis. Our understanding of the effects of hemoglobin and heme on pulmonary vasculature has expanded because of the study of hematological models of chronic lung disease, and proper management of the lung can improve outcomes of the hematological disorders.

Lastly, Taher and Cappellini discuss organ damage, which results from poor iron control starting in youth, and extramedullary

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hematopoiesis, both of which greatly affect the survival and quality of life in transfusion-dependent and -nondependent adults with thalassemia syndromes.

These reviews underscore the good news that survival is significantly improved in hemoglobinopathies and the bad news that survival is significantly improved, putting patients at risk for new complications that result from their underlying disorder and the aging process.

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