

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Cyclic and Chronic Neutropenia: An Update on Diagnosis and Treatment

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H&O What are the characteristics of cyclic neutropenia and chronic neutropenia?

DD Cyclic neutropenia is a rare disease in which neutrophils and other white blood cell counts fluctuate, usually on a 21-day cycle. When the neutrophil count is low—and it can go down to 0 cells/ μ L—patients are very susceptible to infections. It is a terrible disease because patients are at risk of contracting a severe or even life-threatening infection every 3 weeks throughout their lives. Cyclic neutropenia is an autosomal-dominant disease. Multiple family members in each generation can have the disease; sometimes half the members of a family are affected. Neutropenia and its associated infections and risk of death lead to substantial medical care and hospitalization.

The cause of cyclic neutropenia is almost always a mutation in *ELANE*, the gene that encodes neutrophil elastase. This gene is for an enzyme that is produced and packaged in the primary granules of neutrophils. The mutation causes the production of an abnormal protein that damages the cells as they develop, leading to a failure of cell production. Among the many different mutations that can occur, some are associated with cycling of blood counts. This manifestation is probably a milder abnormality than that associated with severe congenital neutropenia, in which mutations are so severe that patients have very low blood counts all the time.

Chronic neutropenia—neutropenia that lasts for weeks, months, or years—has a number of other causes. In some patients, it is due to a congenital disorder; we know of several mutated genes that can be detected. In other patients, it is an acquired disorder that is not yet well understood. The acquired conditions are much more common. The most common is chronic benign neutropenia of childhood, which may be an autoimmune disease. Chronic idiopathic neutropenia in adults is also acquired. It occurs predominantly in adolescent girls and women, beginning at approximately age 15 and usually lasting, in terms of its initial onset, until the mid-30s. The pattern is similar to that of lupus and some other autoimmune diseases, but it is not a predecessor of those diseases.

H&O What are the symptoms of neutropenia?

DD The symptoms of neutropenia, regardless of its cause, are similar. The first symptoms are fever and signs of infection. The physician should examine the patient to find out where the bacteria have entered the body. When blood counts are low, the patient is more susceptible to infections, which are usually caused by surface organisms. A break in the skin or the mucosa of the gastrointestinal tract will allow penetration of bacteria, and the neutrophils are too few to act as the first line of defense to prevent infection. Treatment with antibiotics can select out tougher organisms—particularly Gram-negative organisms and resistant *Staphylococcus aureus*—that create worse problems.

The symptoms of infection are the usual ones: fever, malaise, and upper respiratory symptoms. A skin abscess or boil is also common. Patients can develop more severe symptoms, such as bacteremia; seeding of abscesses in deep tissues in the body, such as the liver or lung; pneumonia; and gastrointestinal disorders. Perhaps the worst outcome occurs when neutropenia leads to ulcers in the mouth and along the gastrointestinal tract, allowing the

development of *Clostridium* bacteremia. This serious condition has been associated with fatality in many cases.

H&O Are there risk factors for cyclic neutropenia or chronic neutropenia?

DD Presently, we do not know the cause of the genetic mutations that result in cyclic neutropenia. The best evidence suggests that the mutations occur spontaneously. Cyclic neutropenia occurs in people of all racial and ethnic groups around the world. It is also unknown why chronic neutropenia occurs. The acquired diseases that hematologists see are unpredictable in their onset. We have not identified, for example, an immunotype, human leukocyte antigen type, or blood type that predisposes to these illnesses. Chronic neutropenia can also be a feature of other diseases and infections; in the 1990s, HIV infection was a common predisposing cause. It is not understood, however, how a viral infection could trigger chronic neutropenia. In some patients, an autoimmune disease can trigger a T-cell response. Neutropenia can develop in patients with large granular lymphocyte syndromes, and this condition might be a predisposing factor.

H&O How are these conditions managed?

DD For many years, the risk of infection associated with neutropenia was managed with close observation and antibiotics administered at the first sign of infection, which was usually a fever. In a patient with a low neutrophil count and a fever, most doctors would initiate antibiotics as promptly as possible, even before the exact cause was known. This approach is still the cornerstone of treatment.

In the late 1980s, management of neutropenia expanded with the development of the hematopoietic growth factors: granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (G-MCSF). Over time, we learned that G-CSF is the natural regulator of the level of neutrophils in the body and is a very potent stimulus for neutrophil formation. It works in a variety of settings where neutropenia occurs, and it is far more potent than G-MCSF. It has been a real boon to patients with this rare disease. The variety of syndromes that cause congenital neutropenia, chronic idiopathic neutropenia, and benign neutropenia of childhood can also be treated with G-CSF.

Currently, management of patients with chronic neutropenia who have recurrent infections or fever—or who may develop these symptoms—involves administration of G-CSF on a daily, alternate-day, or twice-a-week basis to stimulate and maintain a higher neutrophil level. The clinical characteristics of these patients vary, and the dose must be carefully adjusted to match their capacity to produce neutrophils in response to treatment. The dose is

usually titrated to match the patient's blood circumstances and to boost the neutrophil level up to approximately 1,000–2,000 cells/ μ L. G-CSF has been a very effective preventive treatment for at least 90% of patients with chronic neutropenia. We do not have good alternate therapies, except for bone marrow transplantation, which of course is a complex therapy and requires a suitable donor.

H&O What novel treatments are in development?

DD The novel treatments go hand in hand with understanding the disease mechanisms and finding ways to target them. My colleagues and I recently published a study in *Blood* examining the use of a targeted therapy, the CXCR4 antagonist plerixafor (Mozobil, Genzyme), for a rare cause of chronic neutropenia known as myelokathexis or WHIM syndrome (for warts, hypogammaglobulinemia, infections, and myelokathexis). This drug shows promise in the way it raises blood counts, including both neutrophils and lymphocytes. We are planning clinical trials to test long-term effectiveness.

Studies are under way to explore the hypothesis that blocking the effect of the mutated gene might impair its ability to damage cells and cell production. In other diseases, research of this approach is in various stages of development. The next few years will be exciting as we attempt to develop specific, targeted therapies for patients with these conditions.

H&O What are some other areas of research?

DD One of the biggest questions is why some people with chronic neutropenia have disorders that predispose to leukemia. The underlying mechanisms for leukemic evolution are not known, but patients with severe congenital neutropenia caused by mutations in neutrophil elastase or genes such as *HAX1* develop leukemia at a high rate. We estimate that the lifetime risk is approximately 20–30%.

There are also opportunities for research on the basic causes of neutropenia. We know now that several genes can be mutated to cause neutropenia, but we do not know all of the mechanisms or all of the genes, and much research is focused on these areas. G-CSF has been a very effective therapy, but we would like to find other widely applicable ways to treat neutropenia.

Suggested Readings

Dale DC, Link DC. The many causes of severe congenital neutropenia. *N Engl J Med*. 2009;360:3-5.

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