Neutropenia: Causes. Consequences and Treatment

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Neutrophils, or polymorphonuclear leukocytes (PMNs), are the body's first line of protection and response to bacterial and fungal infections. These cells are formed in the bone marrow from hematopoietic stem cells and reach the blood with many mechanisms for killing microorganisms. At a site of infection, neutrophils ingest the invader, contain it in an internal vacuole and use hypochlorous acid as a key microbicidal substance.

The formation of neutrophils, like the formation of other blood cells, is governed by regulatory cytokines. Granulocyte colony stimulating factor (G-CSF) is the key regulator of neutrophil formation. Normally it maintains a steady level of neutrophil production and blood levels of the cells in a range between 1.8 and 7.0 x 10^9 / L.

Neutropenia has many causes. Four categories are: hematological diseases (leukemia, aplastic anemia, etc) drugs (cancer drugs and all other drugs and many chemicals), autoimmune diseases (systemic lupus erythematosis, rheumatoid arthritis, etc) and infectious diseases (HIV, tuberculosis, measles, etc). Regardless of the cause, neutropenia predisposes to infections. In many patients there are additional risk factors that make infections likely to occur such as older age, co-existing diseases, and immunosuppressive drugs.

Cancer chemotherapy is a common cause for neutropenia, and neutropenia is often the limiting factor for chemotherapy. In these patients, febrile neutropenia is managed primarily by prompt antibiotic therapy and good supportive care. Antibiotics can be used to try to prevent infections in neutropenic cancer patients, but the effects are limited. In the early 1990's randomized clinical trials first showed that the duration of neutropenia after chemotherapy can be shortened and infections prevented with the treatment with G-CSF. Based on a series of randomized controlled trial, clinical guidelines were developed for the appropriate use of this kind of supportive care.

Severe chronic neutropenia is a much less common problem, but it leads to a lifetime of recurrent infections. Cyclic neutropenia is a rare and interesting disorder in which severe neutropenia recurs every 21 days. It is now known to be due to mutation in on of the proteins normally packaged in the primary granules of neutrophils, the protein called "neutrophil elastase or ELA 2. Severe congenital neutropenia, a similar but usually more severe disease, may be cause by mutation in the ELA 2 gene or another gene called HAX 1. A mutation in either of these genes causes neutrophil production to be inefficient because of a loss of cells during their development due to apoptosis. Cyclic and

congenital neutropenia can be treated with G-CSF on a long term basis. Irrespective of treatment, patients with severe congenital neutropenia, like some other congenital marrow disorders, are at risk of evolving to acute myeloid leukemia. Many researchers are currently trying to understand the basis for this problem.

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