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Role of Neukine in precaution and cure of Neutropenia

Neutropenia is a blood disorder that can affect any person. Some people are born with it. It can happen after a viral infection. In some cases, the cause can be a side effect of a drug, or exposure to certain poisons. People can get neutropenia when treated for cancer with chemotherapy drugs. Sometimes it happens for no known reason and severely compromises innate immunity.

Risk of developing fever with severe neutropenia increases approx. 10% per day. Mortality due to infections is about 10-30%

Pathophysiology: Mature neutrophils are produced by precursors in the bone marrow. The total body neutrophil content can be divided conceptually into bone marrow, blood, and tissues. In marrow, neutrophils exist in the form of myeloblasts, promyelocytes, myelocytes, metamyelocytes, bands, and polymorphs. Neutrophils leave marrow storage and enter the blood without re-entry into marrow. In blood, two compartments are present –marginal compartment and circulating compartment. Some neutrophils do not circulate freely (marginal compartment) but are adherent to vascular surface, and these constitute approximately half-total neutrophils in the blood compartment.

Neutrophils leave the blood pool in a random manner after 6-8 hours and enter the tissues, where they are destined for cellular action or death. Thus, if the process producing neutropenia is unknown, measurements of the blood neutrophil number, Absolute Neutrophil Count (ANC), often must be supplemented by bone marrow examination to determine whether adequate production of neutrophils or increased destruction of neutrophils exists.

The term neutropenia describes the situation where number of neutrophils in the blood is too low. Neutrophils are very important in defending the body against bacterial infections, and therefore, a patient with very few neutrophils is more susceptible to bacterial infections.

Everyone has been sick with an infection at one time or another. That is because it's easy for bacteria and viruses that cause infections to get inside the body. Healthy people don't often get infections even though bacteria and viruses are all around them.

The body protects itself against constant risk of infection by making many neutrophils. They are the main defence against infections. People with neutropenia get infections easily and often. Most of the infections occur in lungs, mouth and throat, sinuses and skin. Painful mouth ulcers, gum infections, ear infections and periodontal disease are common. Severe, life-threatening infections may occur. Often the child or adult must be hospitalized and receive intravenous antibiotics. Blood tests are done to find out the status of neutrophils.



The level of neutropenia may vary considerably. In general, blood of healthy adults contains about 2000 to 7000 neutrophils per mm^3 . In children, less than 6 years of age, neutrophil count may be lower. The severity of neutropenia generally depends on Absolute Neutrophil Count (ANC) and is described as follows:

- **Grade I neutropenia:** when the ANC falls below a lower limit of 2000 per mm^3
- **Grade II neutropenia:** when the ANC falls below 1500 per mm^3
- **Grade III neutropenia:** when the ANC falls below 1000 per mm^3
- **Grade IV neutropenia:** When ANC falls below 500 per mm^3

The duration of neutropenia may be short lived. In short-lived cases, the patient is described as suffering from acute neutropenia. However, if a patient has neutropenia for a longer period, i.e. greater than three months, he/she is described as suffering from chronic neutropenia.

Symptoms, experienced by patients, depend on the level of neutropenia. The lower neutrophil count, the greater is the risk of infection. This risk increases if low neutrophil counts persist for more than three days. Types of infection include Otitis Media; Tonsillitis; Sore Throat; Mouth Ulcers; Gum Infection and Skin Abscesses. Any fever (body temperature above $38.5^\circ\text{C}/101.3^\circ\text{F}$) must be taken very seriously and physician should be informed.

Severe neutropenia can lead to serious problems, which require prompt care and attention as the patient could potentially develop a bacterial, fungal or mixed infection at any time. These infections can be life threatening when patient is persistently severe neutropenic and it is therefore important that, if patient develops any signs or symptoms of an infection, then he/she should be seen by a doctor as soon as possible and treated with medications to fight the infection (such as antibiotics).

Consequences of Neutropenia

- 1) **Infection**
- 2) **Hospitalization**
- 3) **Usage of Antibiotics**
- 4) **Chemotherapy dose delays/reductions**
- 5) **Reduced treatment effectiveness of chemotherapy**
- 6) **Reduced QOL**
- 7) **Increased cost of treatment**

Congenital Neutropenia

There are several forms of congenital neutropenia varying in the severity of reduction of neutrophil counts and associated clinical problems. In one severe form, congenital agranulocytosis or Kostmann's syndrome, neutrophils are severely reduced from birth, often to less than 100 per mm^3 . When severe hypoproliferative anaemia or significant thrombocytopenia is seen in neonates and very young children, other diagnoses such as congenital aplastic anaemia should be considered.

Cyclic Neutropenia

A regulatory defect at haematopoietic stem cell level leads to oscillations in production of all types of blood cells. In most patients with cyclic neutropenia, blood neutrophil counts oscillate between mild and severe neutropenia, with counts usually of 100 per mm³ for three to six days with every cycle. It is during these severely neutropenic periods that these patients are particularly predisposed to fever and infection.

Chronic Idiopathic Neutropenia

Chronic idiopathic neutropenia is a general term for cases of severe chronic neutropenia not clearly falling into the cyclic or congenital categories. These patients are described as having normal neutrophil counts earlier in life and an acquired pattern of recurrent problems with infections. **Radiation induced neutropenia** is related to the amount of exposure and if the site is an area carrying bone marrow (such as the sternum or skull). **Febrile Neutropenia (FN)** is a relatively frequent event in cancer patients treated with chemotherapy. FN is defined as fever > 38.2 degree for more than 1 hour associated with ANC of 500–1000 cells/mm³ or less. The incidence of FN with common regimens is 25-40% in treatment naïve patients.

It is a potentially life threatening situation and requires prompt medical intervention. The standard treatment includes supportive care plus broad-spectrum antibiotics. Haematopoietic growth-stimulating factors are a class of cytokines that regulate proliferation, differentiation, and functions of haematopoietic cells. Among them, the granulocyte colony stimulating factor (G-CSF) and the granulocyte macrophage colony-stimulating factor (GM-CSF) have been studied in cancer patients because of their potential effect on neutropenia. G-CSF regulates the production of neutrophil lineage. The administration of G-CSF to humans results in a dose-dependent increase in circulating neutrophils mainly because of a reduced transit time from stem cell to mature neutrophil.

Risks of neutropenia in cancer:

- 1) **High dose regimen-breast cancer , Non-Hodgkins lymphoma, Hodgkin disease, Small cell lung cancer**
- 2) **Polychemotherapy in drug resistant tumour**
- 3) **Neutropenia occurred in previous cycle of chemotherapy.**
- 4) **Myeloablative chemotherapy with SCT**

Approaches in neutropenia:

Primary prophylaxis – G-CSF is given well in advance as primary prophylaxis to prevent the occurrence of neutropenia in such known situations where the risk of FN is > 40% like with high dose regimen for Ca Breast, NHL, HD, SCLC patients, BMT, dose intensification, survival benefits in elderly.

Secondary prophylaxis – If neutropenia occurred in previous cycle of chemotherapy, G-CSF is given as secondary prophylaxis to prevent it's occurrence in next cycle of treatment.

Prior to G-CSF, dose reduction and delay in cycles were only solutions for prevention of neutropenia.



Treatment of neutropenia:

The treatment of neutropenia depends on its cause and severity. Drugs that may cause neutropenia are discontinued whenever possible, and exposures to suspected toxins are avoided. Sometimes the bone marrow recovers by itself without treatment.

People who have severe neutropenia can rapidly succumb to infection because their bodies lack the means to fight invading organisms. When these people develop infections, they are generally hospitalized and immediately given strong antibiotics, even before the cause and exact location of the infection are identified. Fever, the symptom that usually indicates infection in a person who has neutropenia, is an important sign that immediate medical attention is needed.

Growth factor (cytokines), granulocyte colony-stimulating factor (G-CSF) is widely used to prevent fever and infections in patients with severe neutropenia (e.g., after bone marrow transplantation and intensive cancer chemotherapy). Cytokine therapy is expensive; however, with the risk of febrile neutropenia this remains the only solution. In general, most clinical benefit occurs when G-CSF is administered about 24 h after the completion of chemotherapy. Doses of 5 µg/kg/day sc are often effective. G-CSF accelerates the return of the neutrophil count to > 500/µL in patients undergoing autologous bone marrow transplantation or intensive chemotherapy.

Corticosteroids may help if the neutropenia is caused by an autoimmune reaction. Antithymocyte globulin or other types of therapy that suppresses the activity of the immune system may be used when a disease such as aplastic anaemia is present. Removing an enlarged spleen may cure the neutropenia involved with hypersplenism.

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