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Management of Neutropenia in Cancer Patients

Maryam B. Lustberg, MD, MPH
Assistant Professor, College of Medicine, The Ohio State University, Columbus, Ohio

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How common is neutropenia among cancer patients?

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The majority of cancer patients develop neutropenia, most often due to chemotherapy. Neutropenia can also be caused by solid tumor malignancies, if they infiltrate the bone marrow, or by certain lymphoproliferative malignancies, such as natural killer cell lymphomas (large granular lymphocytic leukemia), hairy cell leukemia, and chronic lymphocytic leukemia (CLL). Radiation, if it is administered to multiple sites of active bone marrow proliferation, can cause neutropenia. There are also less common autoimmune etiologies and rare genetic, congenital, or monoclonal pathologic etiologies for neutropenia that can occur in patients with and without cancer, for example, aplastic anemia, paroxysmal nocturnal hemoglobinuria, May-Hegglin anomaly, rheumatoid arthritis (RA), and systemic lupus erythematosus. The soluble Fas ligand mediates the apoptosis of neutrophils in large granular lymphocytic leukemia, whereas the autoimmune etiologies are associated with increased levels of circulating antineutrophil antibodies with accelerated neutrophil apoptosis. Felty's syndrome is an RA-associated neutrophilia, perhaps exaggerated by hypersplenism. Viral (CMV, EBV, HIV, etc), parasitic (malaria), and malignant etiologies for hemophagocytosis should also be considered in the differential diagnosis when neutropenia is associated with other cytopenias. Finally, cancer and non-cancer patients alike may develop antibiotic-induced isolated neutropenia with the bone marrow aspiration revealing maturation arrest of the myeloid lineage. This is immediately reversible upon discontinuation of the antibiotic (eg, penicillin agents, beta-lactam antibiotics). One should also be aware of the genetic predisposition for isolated neutropenia present in some African Americans and the occurrence of fluctuating cyclical neutropenia in cyclic neutropenia.

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How is the diagnosis of neutropenia made in cancer patients?

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Most neutropenia is diagnosed by a routine complete blood count (CBC), with the accompanying differential count yielding a decrease in the absolute number of neutrophils. Mild neutropenia is defined as an absolute neutrophil count (ANC) of less than 1,500 cells/mm^3. A count less than 1,000 cells/mm^3 is considered moderate. Less than 500 cells/mm^3 represents the severe degree of neutropenia.

Patients may or may not have signs or symptoms of neutropenia or a decreased ANC. In some patients, if the neutropenia is associated with thrombocytopenia and anemia, the clinical manifestations will more frequently consist of bruising and decreased stamina, and the ANC abnormality will be an incidental finding. Patients with isolated neutropenia may not have any specific symptoms. A fever may be the first sign.

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What are the risk factors for the development of neutropenia in cancer patients?

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Risk factors include older age, comorbidities, and a history of multiple cytotoxic chemotherapy regimens. The type of chemotherapy can also be an important risk factor for neutropenia. For example, longer durations of neutropenia have been associated with bone marrow transplantation and chemotherapy for hematologic malignancies, whereas many of the chemotherapy agents for solid tumor malignancies are associated with a shorter duration of neutropenia. Certain malignancies are associated with neutropenia and lymphopenia as part of the disease process, which can become exacerbated by ongoing therapy. The differential diagnosis of neutropenia in these conditions always includes a worsening disease process and new occult infection in addition to neutropenia caused by treatment.

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What are the consequences of neutropenia in cancer patients?

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Fever during neutropenia can be a very serious consequence. Patients with febrile neutropenia are at high risk of increased mortality, and this neutropenic complication is considered to be an oncologic emergency. The most serious infections occur with gram-negative bacteria, which can be life-threatening; however, gram-positive bacterial infections, fungal infections, and viral infections always generate significant morbidities and possible mortality in the immunocompromised neutropenic host. In patients without fever, neutropenia can lead to chemotherapy administration delays and, eventually, dose modification. Such alterations to therapy may have long-term consequences in terms of the cancer outcome in patients being treated with curative intent but not in the metastatic setting.

Another serious complication of neutropenia is neutropenic colitis, also known as *typhlitis*. Patients present with fever and abdominal pain. Patients are treated with antibiotics and conservative management, but they may need acute surgical intervention if there is concern for the ischemic bowel. This condition is more common in hematologic malignancies with longer periods of neutropenia.

The Multinational Association of Supportive Care of Cancer (MASCC) risk-index score is a validated tool that can help clinicians predict which patients presenting with febrile neutropenia are at low or high risk of developing complications. The tool contains 8 factors that can be quickly assessed upon presentation of febrile neutropenia. Patients with a score

of 21 or greater are considered low risk, and patients with lower scores are considered higher risk and need more intensive management. Poor predictors of prognosis include age older than 60, moderate symptoms with febrile neutropenia, hypotension, dehydration, inpatient status, and prior fungal infection.

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Are there any preventive measures?

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Neutropenia with certain drug regimens is not preventable, but additional measures can be taken to prevent serious complications of neutropenia. The duration of neutropenia can be minimized with the use of granulocyte colony– stimulating factors (G-CSFs) in appropriately selected patients. The National Comprehensive Cancer Network has published guidelines on the use of myeloid growth factors. Patients who are at high risk of neutropenia (>20% risk of developing febrile neutropenia) prior to the start of their treatment regimen or who are receiving a chemotherapy regimen that is associated with a high risk of neutropenia benefit from the use of G-CSFs. Among patients at intermediate risk (10–20% probability), individualized consideration of the need for growth factor support with discussion between the patient and physician is needed. Patients at low risk (<10% risk) do not benefit from routine use of G-CSFs. Patients receiving G-CSFs will still nadir with chemotherapy, but they will spend fewer days at the lowest count range than without treatment, thus decreasing the chance that infectious complications—the most feared outcome—will occur. Other preventive approaches consist of chemotherapy dose reductions and dosing interval modifications. In general, with these strategies, the majority of patients are able to safely receive and complete the chemotherapy regimen of choice for their malignancy. In select cases, if a patient's history suggests an inability to tolerate a very intensive chemotherapy regimen, then another preventive measure is to select a less intensive regimen.

Due to the wide variability in the responses of patients to chemotherapy, there is ongoing need to understand the pharmacogenomics of chemotherapy drugs in order to help identify patients who may be at increased risk of developing neutropenic complications. Ongoing research is searching for single nucleotide polymorphisms in genes involved with drug-metabolizing enzymes and drug transporters. Identification of critical SNPs may help to create a "signature," which could be applied to clinical settings to determine who will be predisposed to develop significant chemotherapy-induced neutropenia. However, at this time, this testing is done only in the research setting, and additional work is needed before it becomes a standard clinical test.

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When is treatment necessary?

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Treatment is required when neutropenia is associated with fever because the body may not be able to effectively fight an active infection that occurs during this time. Hospitalization is

advisable for the majority of patients with febrile neutropenia. Broad-spectrum antibiotics are quickly initiated, and the patient is observed until the neutrophil count recovers.

Hospitalization might not be prolonged, but will depend on the duration of neutropenia. Patients with hematologic malignancies tend to require longer hospitalization. In general, most patients can be safely discharged when their neutrophil count is greater than 500 and no clear source of infection has been found.

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How is neutropenia managed in cancer patients?

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Neutropenia is managed by chemotherapy dose modification, dose interval delays, and/or initiation of primary prophylaxis with recombinant G-CSFs in appropriate patients based on individualized febrile neutropenia risk assessment of the patient and of the chemotherapy regimen. The oldest G-CSF is filgrastim (Neupogen, Amgen), which is administered daily via injection during neutropenia. A longer acting G-CSF is pegfilgrastim (Neulasta, Amgen). The most recently FDA-approved G-CSF is tbo-filgrastim (Neutroval, Sicor Biotech), a filgrastim biosimilar. All agents are well tolerated. Most importantly, the duration of severe neutropenia, the depth of the absolute neutrophil count nadir, and complications associated with febrile neutropenia are all significantly reduced.

There is ongoing research for new myeloid cell line growth agents, but just as important has been the emphasis on developing clinical assessment tools, which can be applied to more accurately “risk-stratify” patients with neutropenia and febrile neutropenia. Examples of such tools are being validated in prospective clinical trials examining patients with febrile neutropenia to determine who can be safely managed with close follow-up in the outpatient setting versus which patients will require hospitalization.

Generally, there is no role for corticosteroids in neutropenia management in cancer patients. In patients with septic shock with or without neutropenia, corticosteroids may be indicated. In addition, alternate-day dosing of corticosteroids has been used in patients without malignancy who have human cyclic neutropenia.

Intravenous immunoglobulin (IVIG) therapy is not indicated for patients with febrile neutropenia as a consequence of chemotherapy. IVIG therapy has been used for autoimmune and chronic neutropenias unrelated to chemotherapy.

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Do cancer patients pose particular treatment challenges?

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Patients are very frightened by the prospect of neutropenia, so additional education on this topic can be helpful. Sometimes they are unsure of what activities should be avoided to minimize infectious complications during neutropenia. Our thinking about neutropenia has

changed in recent years. Neutropenic precautions now depend on the degree of neutropenia and the type of cancer. Good hand hygiene is very important. In patients with prolonged neutropenia as experienced during hematologic malignancies and bone marrow transplantation, minimizing exposure to pets and live plants is recommended during periods of profound neutropenia. However, in solid tumor malignancies, most patients do not experience very long periods of neutropenia, and these precautions are more relaxed. A recently published Cochrane review on the benefit of a low-bacterial diet was not conclusive regarding evidence for or against recommending this approach. It is very important that each patient discuss these precautions with his or her doctor so that they can be tailored to specific needs.

It is very distressing for cancer patients to develop febrile neutropenia and to require frequent hospitalizations. This outcome tends to occur with the first cycle of chemotherapy, and it can be quite challenging because patients become frightened about what future cycles of chemotherapy will be like. Anything we can do to safely prevent febrile neutropenia is beneficial.

Suggested Readings

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