

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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## Prevention and Treatment of Chemotherapy-Induced Neutropenia



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### **H&O** How common is chemotherapy-induced neutropenia, and which patients are at risk?

**JC** Neutropenia is a lowering of the neutrophil count that happens in almost all patients getting chemotherapy. In fact, the development of cytotoxic chemotherapy over the last 40 years—the schedules and the doses—is based on neutropenia. Neutropenia is usually the dose-limiting side effect, so it determines the dose of chemotherapy we give.

Because not all patients are the same, however—they metabolize the chemotherapy differently—some patients are going to have excessive amounts of neutropenia compared with others. We try to develop regimens that are in a safe range for most patients, where the risk of severe neutropenia is low. But even in the low-risk regimens, some patients are outliers who develop neutropenia and complications from it.

A patient whose neutrophil count drops below 1,000 or below 500 has high-risk neutropenia: grade 3 or 4. At this level, there is a risk of developing a fever or infection. Essentially, for each day a patient's neutrophil count is below 500, the risk of developing febrile neutropenia is about 10%. Regimens that are more myelosuppressive are the ones that are more associated with this.

A low-risk regimen is defined as a regimen where there is less than a 10% risk of febrile neutropenia. Most of the standard regimens fall into this category, although some regimens have a 10–20% risk and others have a risk of greater than 20%.

If the risk of neutropenia is greater than 20% with a given regimen, we recommend first-cycle prevention strategies. This would be the use of a myeloid growth factor, which we also call a granulocyte colony-stimulating factor (G-CSF) agent. If the patient is unable to take one of these,

you might have to do a dose reduction or alter the treatment in some other way.

### **H&O** What are the effects of neutropenia on patient outcomes?

**JC** This is an interesting question. It turns out that the effects are 2-fold, good and bad.

Problems occur when patients develop neutropenia to the point that they end up with a fever and an infection, in which case they need to be hospitalized. Unfortunately, there is a mortality risk for these patients. The risk is low for patients who have uncomplicated febrile neutropenia—maybe a few percent—but obviously, any death from a treatment complication is not really acceptable. The risk increases substantially for patients who have a lot of comorbidities, such as lung cancer patients who have lung disease or heart disease. These patients are often older, and the risk of developing fatal pneumonia is more substantial—maybe as high as 8% or 10%.

A more extreme example would be a patient with acute leukemia who starts out with a very impaired hematopoietic system, and the treatments we give lead to neutropenia that lasts for weeks rather than days. Patients with leukemia are much more likely to die of complications of the treatment, especially if they are older. Women who receive adjuvant chemotherapy for breast cancer also are at fairly high risk of developing febrile neutropenia because of the regimens that are used. Fortunately, the risk of dying is very low for women who are younger and healthier, but it still can happen.

Although the biggest risk from febrile neutropenia is the risk of dying from complications, there are also downstream effects. For example, patients may have a reduction

in chemotherapy dosing, or their next treatment may be delayed until they can recover from an infection. As a result, they get a lower total dose of treatment—reduced relative dose intensity. Getting less treatment than what we would have ideally prescribed may reduce their survival from their cancer. This risk is not as well defined, although it has been studied in both lymphoma and adjuvant chemotherapy.

### H&O What are the other effects of neutropenia?

**JC** It turns out that neutropenia—not with fever necessarily, but just a measurement of neutropenia to a certain level—is a biomarker of benefit of chemotherapy.

Cytotoxic chemotherapy affects cell division of the white blood cell precursors, resulting in neutropenia. In fact, there are fairly consistent data showing that patients who develop neutropenia from chemotherapy have better survival than patients who do not develop it. One way to look at it is this: if you give enough chemotherapy to cause neutropenia, you are probably giving enough chemotherapy to have the greatest cytotoxic effect against the cancer as well—but only if you manage the neutropenia to avoid putting the patient at risk for infection and other complications.

The goal should be to create modest neutropenia, but nobody has shown exactly how much. For example, if you get a neutrophil count of 1,000 as your lowest point—which is grade 3 neutropenia—you are unlikely to develop a fever. Studies have shown that people with grade 3 neutropenia have better survival than patients who have grade 1 or 2 neutropenia, or no neutropenia.

The reason that some patients get neutropenia and others do not at the same delivered dose of chemotherapy is complicated, but is related to the fact that we do not have an ideal way to determine the correct dose of chemotherapy. We determine the “proper dose” by factoring in such things as the patient’s height and weight, but those are just 2 factors that affect how people metabolize the chemotherapy. Age, kidney function, and all sorts of other parameters probably affect pharmacokinetics and pharmacodynamics.

### H&O Is it better to prevent or treat neutropenia?

**JC** I have been preaching for a long time that prevention is better. If you can identify the patients at risk and just target them for prevention, you can dramatically reduce hospitalizations and mortality. Patients who do not have severe neutropenia may have a better quality of life; they do not need to worry as much about being out in crowds, or spending time with their family. And of course, the ability to deliver standard therapy more safely has a potential impact on outcomes.

We do have agents that can help prevent severe neutropenia, but there is expense associated with those agents. When the risk of febrile neutropenia is greater than 20%, CSFs can be considered. However, others have advocated chemotherapy dose reduction as an alternative strategy, as in a 2012 article in the *Journal of Clinical Oncology* by Schnipper and colleagues on ways to improve care and decrease costs. But the fact is that the impact of dose reduction on outcomes has not been well studied. If we were to just reduce the dose of chemotherapy in everybody, we probably would lessen the benefit of chemotherapy. This needs to be studied prospectively.

### H&O What prevention and treatment regimens are used for neutropenia?

**JC** There are 3 approaches to prevention: dose reduction; prophylactic antibiotics in a selected population; and CSF agents.

With dose reduction, you single out patients who seem to be at high risk for febrile neutropenia or other complications and alter their regimen. Dose reduction has been a standard approach to reducing neutropenia for decades, with the caveats previously mentioned.

As for antibiotics, prophylactic antibiotics can be given during the time when people have a low white blood count and neutropenia tends to set in. Antibiotics can prevent some infections and reduce the severity of an infection that sets in. The usefulness of this approach has been best proven in high-dose chemotherapy regimens with bone marrow transplant, where they reduce the risk of infection but do not eliminate it. There is also at least some benefit in other patients with solid tumors and in those with lymphoma, but you have to treat a lot of patients to see a benefit in a very small number. The problem with this approach is that you are exposing many patients to antibiotics they might not need, and the antibiotics may lead to antibiotic drug resistance in either those patients or in the population at large. Because of that, most of the guidelines committees do not recommend the use of prophylactic antibiotics, particularly in the outpatient solid tumor or lymphoma patient population. Their use is restricted more to the high-risk patient populations where they are likely going to be getting antibiotics regardless.

As for CSF agents, the major regulator of neutrophil production is G-CSF. G-CSF is an endogenous hormone in our bodies that normally helps regulate white blood cell count in times of stress and infections. G-CSF levels will go up in response to infection or low white blood cell count. If your white blood cell count falls, G-CSF levels in the body rise and help restore your white blood cell count. The problem is that it takes several days for that to kick in.

## H&O What types of CSFs are available?

**JC** CSF agents are agents that essentially stimulate the production of neutrophils from the bone marrow in advance of when they would normally form. The ones that are available in the United States are the G-CSFs filgrastim (Neupogen, Amgen) and pegfilgrastim (Neulasta, Amgen), and the granulocyte-macrophage-CSF sargramostim (Leukine, sanofi-aventis). If we wait until the patient is neutropenic and then we give a CSF, this is a little too late. On the other hand, if you give it after chemotherapy, there is a window of time a few days after chemotherapy before blood counts begin to fall and that is enough time to drive production of early myeloid cells to become neutrophils. So, you can lessen or eliminate the low white blood count through the use of these prophylactic growth factors.

Filgrastim and sargramostim are daily-administered agents that have a relatively short half-life because of clearance by the kidneys. Pegfilgrastim has longer-acting molecules that are pegylated; they have polyethylene glycol attached to the G-CSF so that the drug stays in circulation and does not get cleared by the kidneys. A single dose will stay in the circulation to drive production of new neutrophils. And then as those neutrophils are produced, the pegged G-CSF will be cleared by the neutrophils themselves. The neutrophils have receptors on them for the G-CSF. We can choose daily dose or single dose, depending on the situation. In addition, biosimilar agents are being developed; these will expand the market for the agents available both in this country and worldwide.

## H&O What are the criteria for using CSFs?

**JC** The guidelines are pretty consistent between the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the European Society of Clinical Oncology. All of the guidelines focus on people whose risk is at least 20%, so if the physician thinks that the patient has a 20% or greater risk of developing febrile neutropenia at some point during their clinical course with whatever chemotherapy regimen is planned, they should get first-cycle prophylaxis with a G-CSF agent.

Several factors go into determining risk. First and most obvious are the disease state and the chemotherapy regimen being used. In addition, there are personal factors that may alter the risk. If the chemotherapy risk is normally 10% across 100 patients, it may be above 20% for a patient who is 75 years old or has significant comorbid disease. You have to put this in the context of personalizing treatment for the patient. Although there are some

guidelines to help determine a patient's risk, a lot of it still falls to personal judgment. The most common personal factor that relates consistently to a patient's risk is age. For most intermediate regimens, patients who are older than 65 or 70 years will be at elevated risk—a 20% or greater risk. We will generally use first-cycle prophylaxis on these patients. Alternatively, we can follow patients closely during the first cycle of treatment and consider using prevention strategies for the second cycle if they develop grade 4 neutropenia, even if they did not develop fever and infection the first cycle.

One of the problems with this strategy is that the risk of fever and neutropenia with most regimens is highest in the first cycle of chemotherapy. This is different than other chemotherapy side effects such as nerve damage or heart damage, which occur as more of a cumulative effect than a first-cycle event. If a particular patient is in fact at high risk because of factors we did not predict such as differences in metabolism, we are going to see the effects of this right away, after the very first cycle. If we do not see severe neutropenia, then we are going to continue the chemotherapy. If we do see it, we can make some alterations in chemotherapy in subsequent cycles, so getting it right up front is important.

## H&O How effective are the CSFs?

**JC** The studies have shown pretty consistently—and a 2007 meta-analysis by Kuderer and colleagues has reviewed these—an approximate 50% reduction in the risk of febrile neutropenia and hospitalization complications across a range of regimens. We thought that these drugs might not be as effective in patients who are at low risk, but they seem to be as effective or more effective in low-risk patients compared with high-risk ones. If you look at the pivotal studies we did years ago in small-cell lung cancer, including a 1991 study in the *New England Journal of Medicine*, the patients with chemotherapy averaged 5 or 6 days of neutropenia in the absence of a G-CSF agent. When patients were given a G-CSF agent, neutropenia was reduced to 3 days. Furthermore, the risk of febrile neutropenia fell from more than 50% to about 20%. Of course, that was a fairly high-risk population.

In a 2005 study by Vogel and colleagues of docetaxel in a population with breast cancer, the risk fell from 17% in the control group to 1% in the pegfilgrastim group. Multiple factors are at work, but it may be that when you reduce the neutropenia from 1–2 days to 0 days, you pretty much eliminate the risk. When you reduce it from 5 days to 3 days, you cut the risk in half, so the duration of neutropenia is what really drives whether patients have this or not. And that seems to be true across solid tumors as well as hematologic malignancies.

## H&O What are the downsides to using these medications?

**JC** Two of the downsides to CSFs are cost and inconvenience. Almost all of these have to be given subcutaneously. It is not really painful, but it is another injection. The injection has to be given starting the day after chemotherapy, which usually means another visit to the doctor's office or injection at home. Those are just practical considerations.

In terms of other risks, one theoretic concern is that these agents might actually cause leukemia because they are white blood cell stimulants. The concern is that they might cause problems in the bone marrow from stimulation of normal white blood cells or maybe abnormal white blood cells. When you look at long-term randomized trials of patients taking or not taking G-CSFs, such as the 2010 study by Lyman and colleagues in the *Journal of Clinical Oncology*, most of the studies find a slightly higher incidence of leukemia or myelodysplasia in patients who get these growth factors versus those who do not. The complicating factor that cannot be sorted out of this is that, in almost all of these studies, the total amount of chemotherapy given was greater in the patients who received the myeloid growth factor versus those who did not. And chemotherapy, unfortunately, is well known to be leukemogenic. So there is a slight excess risk of leukemia in the long term that most likely is associated with chemotherapy dosing.

Still, if you look at the reduction in mortality, the impact is 10-fold higher for mortality reduction than it is for excess cases of leukemia in the CSF-treated patients.

So, these trials suggest that enabling chemotherapy delivery at standard doses through the use of G-CSFs permitted better overall survival. Even though there was a slight increase in leukemia, the leukemia risk was small relative to the overall impact. So, the net risk to benefit ratio is in favor of myeloid growth factors when they are needed. If they are not needed, obviously, we do not want to be using them.

Another possible risk is splenomegaly in children; the spleen sometimes enlarges from these agents and can even rupture. This is pretty rare, but it does happen. There is also the potential for interaction with other drugs, particularly bleomycin—G-CSFs may accentuate the lung injury that can occur with bleomycin. A small percentage of patients get something called Sweet syndrome, collections of neutrophils that look like little abscesses in the skin. These are all very rare events.

A more common side effect is bone pain; the myeloid growth factors stimulate the bone marrow cells and we think that the expansion may cause bone pain. The risk of this has been reported in about 20–50% of patients,

depending on the study. The bone pain can occur in any area, including the back, chest, ribs, or legs. Some patients get bone pain 1 or 2 days after the injection, and some get it a week to 10 days later. Usually it lasts from several hours to a day, and occasionally longer. Bone pain that does not go away after a few hours usually can be alleviated with nonsteroidal anti-inflammatory drugs, although some patients will need mild narcotics for it.

We need to tell patients ahead of time that they may experience bone pain so they are prepared for this.

## H&O Are any other treatments for neutropenia under development?

**JC** We already have the first-generation and second-generation agents. A number of agents that are biosimilar to the existing agents and are in development and some that already available in Europe will eventually become available here. The hope is that these will provide similar benefit at reduced cost. One of these agents that should be available later this year in the United States is tbo-filgrastim.

There certainly are a number of other molecules that simulate neutrophil production, release, or function in other ways; so yes, I think that it is still an active area of research.

## Suggested Readings

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