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Running on Empty

BY MELISSA KNOPPER

Treatment-induced neutropenia hinders ability to fight infection.

After his fourth cycle of chemotherapy for lung cancer, retired Marine Everett VanderVere, 73, who describes himself as a “tough bird,” had to go to the hospital with fever and severe weakness.

VanderVere was among the nearly half of patients receiving chemotherapy who develop neutropenia—the shortage of neutrophils, a type of white blood cell that protects against infection. His doctor gave him a shot of Neupogen (filgrastim), a drug that boosts neutrophil production in the body. “It did the trick,” recalls VanderVere, who lives in Jacksonville, North Carolina. “I felt better in about three days.”

Neutrophils survive only three to five days in the body and function as feisty watchdogs that chase tiny particles of bacteria, viruses and other foreign invaders in the blood. Once they catch the invaders, neutrophils surround them and use potent enzymes to destroy the pathogens.

Traditional cytotoxic chemotherapy drugs, which target rapidly dividing cancer cells, also kill healthy cells in the process, including neutrophils. Fast-growing neutrophils quickly succumb to these chemotherapy drugs. With lowered numbers of neutrophils, seen most commonly during the first cycle of chemotherapy, cancer patients lose the powerful protection neutrophils offer and face an increased risk of infections, which can become life-threatening if untreated. Even if doctors can control an infection with antibiotics, the setback could delay chemotherapy treatments that may impact the patient’s chances of achieving full benefit of chemotherapy and long-term survival. Although chemotherapy is the main cause of neutropenia, it can also result from radiation therapy, especially to the spine and pelvis.

Since fever can be a sign of underlying infection, VanderVere’s oncologist told him to call at the first sign of a fever (temperature of at least 100.5°F). VanderVere recalls how his worried wife kept coming at him with a thermometer. “And wouldn’t you know it, I got a fever,” says VanderVere. His doctor sent him right to the emergency room, where he was admitted for neutropenia.

Beyond a fever (febrile neutropenia), other symptoms of neutropenia are not specific and include fatigue and body aches, which can be seen with many chemotherapy drugs. Physicians usually detect neutropenia by doing routine blood tests, such as a CBC (complete blood count) to determine the number of white and red cells in a patient’s blood. Doctors calculate the number of

neutrophils in the blood by looking at the absolute neutrophil count (ANC), which shows the percentage of white blood cells that are neutrophils. An ANC above 1,500 cells per microliter of blood is usually considered safe, but when the neutrophil count falls below 1,000 cells per microliter, the risk of infection increases somewhat. The risk of infection increases greatly when it falls below 500 cells per microliter. Clinicians will ask patients who fall into this category to take special precautions, such as avoiding crowds and extra hand washing, to prevent infection.

View Illustration: The Role of Neutrophils

Why It Happens

Most traditional cytotoxic (cell-killing) chemotherapy drugs will cause neutropenia. “This is a universal side effect of cytotoxic chemotherapy,” says Duke University oncologist Jeffrey Crawford, MD. “I can only think of a couple of chemotherapy drugs that don’t cause it,” which include Blenoxane (bleomycin), Oncovin (vincristine) and the steroid prednisone. But those compounds are typically used in combination with other cytotoxic drugs, he adds.

Hormonal therapies—such as Arimidex (anastrozole), tamoxifen and Femara (letrozole) for breast cancer, or Lupron Depot (leuprolide) and Zoladex (goserelin) for prostate cancer—do not cause neutropenia. Nor do some of the newer targeted treatments, such as Herceptin (trastuzumab) for breast cancer, Tarceva (erlotinib) for lung and pancreatic cancer and Nexavar (sorafenib) and Sutent (sunitinib) for kidney cancer. These targeted drugs affect specific parts of a cancer cell instead of killing any rapidly dividing cell that crosses its path.

In addition to the type of therapy received, certain risk factors make patients more vulnerable to neutropenia. For example, elderly or diabetic patients are more likely to develop it, says University of Rochester oncologist Gary Lyman, MD. Doctors also watch for liver problems by checking for an elevated bilirubin level before starting chemotherapy. “If the liver is not working properly, the drug will be slow to metabolize and it will have more toxic effects,” says Dr. Lyman.

Certain types of cancer, such as lymphoma and myeloma, typically involve more aggressive treatment, which can increase the odds of neutropenia.

Treatment and Prevention

Neupogen, the injectable drug given to VanderVere, was approved in 1991 and has become the most popular drug to counter neutropenia. Scientists developed it by looking at certain particles in the body that signal white blood cells to grow. By recreating blood growth factors, such as granulocyte colony-stimulating factors (G-CSF), they were able to help patients with neutropenia return to normal white blood cell levels faster. Neupogen, given by injection for five to seven days, can be inconvenient for patients. Neulasta (pegfilgrastim), a newer version of Neupogen approved in 2002, is longer lasting, so doctors only have to give it

every 21 days, if necessary.

View Illustration: Stimulating Growth Factors

These drugs do have side effects, particularly bone pain in the arms, lower back and joints, but many patients feel the pain is worth it because the drugs prevent treatment delay or having to take a lower dose of chemotherapy. Since these growth factors entered the market, they have prevented many infection-related deaths, says Dr. Lyman. They also improve quality of life by keeping patients out of the hospital to continue with their daily activities.

Breast cancer patient Lynn Baker, 54, of Rochester, New York, saw Neulasta as a key ally when she recently went through chemotherapy. The drug—taken preventively—helped her conquer intense doses of Adriamycin (doxorubicin) and Cytosan (cyclophosphamide) every two weeks. “For me, it brought peace of mind,” Baker says. “Just having the confidence of knowing you’re doing well—it makes a big difference.”

Baker’s aggressive treatment, known as dose-dense chemotherapy, involves giving chemotherapy every two weeks as opposed to every three weeks. This altered treatment schedule would not have been possible without growth factors because it normally takes three weeks for white cells to grow back after chemotherapy.

Baker was able to inject her Neulasta treatments at home instead of driving to the hospital each time. Her 24-year-old diabetic daughter helped her with the shots. “I did not have any trouble with it,” she says. “It just kept everything on an even keel for me.”

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—Gary Lyman, MD

The American Society of Clinical Oncology recommends giving blood growth factors preventively if the patient has a 20 percent or greater risk of developing neutropenic complications, such as febrile neutropenia. Yet Dr. Lyman’s research shows too few patients in the high-risk category have access to these helpful drugs because of cost and the difficulty in defining who is at risk. A study in the *Journal of Clinical Oncology* showed more than half of patients with early-stage breast cancer at 1,243 community centers across the country did not receive the full dose of chemotherapy because of neutropenia. Only one-quarter of those patients received growth factor injections, the study found. And few of those injections were given preventively.

“These data were eye-opening to us because we had no idea such a substantial

portion of patients were being undertreated,” says Dr. Lyman. Too often, he says, physicians make assumptions that certain groups of patients, such as the elderly and obese, will not be able to handle a full dose of chemotherapy. When, in fact, studies show both groups can make it through treatment just fine, especially with the prophylactic use of growth factors.

Dr. Lyman and his colleagues created a computer model to help local physicians overcome this challenge. They gathered data from 120 community oncology practices, considering as many as 8,000 different factors as soon as a patient begins treatment. Dr. Lyman and his team of researchers presented the initial model during the 2006 meeting of the American Society of Clinical Oncology in June. The model includes everything from the type of cancer to the type of chemotherapy drugs used to pre-existing medical problems to obstacles in the healthcare system. If validated, they will roll out a working prototype this fall to oncologists across the country. Physicians will be able to use the model on a handheld PDA device into which they can enter a patient’s unique set of factors. “The model will be able to produce an individualized risk estimate for that particular patient,” Dr. Lyman says.

Population studies show patients with fever and neutropenia have a 5 to 10 percent risk of dying. When used preventively, growth factors like Neupogen and Neulasta may cut that risk in half. So, says Dr. Lyman, if oncologists can calculate the risk with more accuracy, more lives can be saved. “Everybody wins if we are able to more accurately calculate the risk.”

What's New

David Dale, MD, and his colleagues at the University of Washington studied a molecule called AMD3100, also known as Mozobil™ (plerixafor), that helps increase the number of early stem cells (or CD34-positive cells) entering the bloodstream. Those cells repopulate the bone marrow, then divide and differentiate to become neutrophils and other types of blood cells.

Dr. Dale’s work showed AMD3100 is more effective when combined with a G-CSF, such as Neupogen or Neulasta. “AMD3100 added to G-CSF actually allowed for larger quantities of stem cells than ever before,” says Dr. Dale. The drug is now in late-phase testing.

Telintra (TLK199) is another promising treatment in the pipeline. During a recent meeting of the American Society of Hematology, scientists reported Telintra has the ability to increase red and white blood cells and may be helpful against neutropenia. It currently is in phase II trials.

To keep on track with chemotherapy, patients must work closely with physicians to prevent neutropenia and watch for infections. For those with known risk factors for neutropenia, it pays to ask about a growth factor before starting chemotherapy, says Baker. “My counts were up, and I knew I could go on through and make each of my treatments on time.”