

ADVANCES IN SUPPORTIVE CARE

Current Developments in Side Effect Management, Palliative Care, and Quality of Life

Update on the Management of Neutropenia

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H&O Why is neutropenia an important concern in the treatment of cancer?

DD Neutropenia is important because it is the primary and dose-limiting toxicity associated with most of the drugs used to treat malignancies for the last fifty years. The use of chemotherapy leads to the risk of low neutrophil counts and infection, and low neutrophil counts can thus lead to reductions in treatment. Less-than-full treatment can translate into a decreased chance of cure or a reduced response to treatment.

H&O Is neutropenia more common with certain treatment regimens?

DD Corticosteroids, which constitute one of the older treatment methods, do not suppress the blood-forming system at all, but they are not used, or used only very rarely, as primary therapies. There are many other drugs that cause transient suppression, and others cause longer-term, deeper suppression of the blood-forming system. Because most chemotherapy drugs are used in combination, knowing the potential toxicities of combinations of chemotherapy is complicated. There are also a few critical drugs currently in use that have greater myelotoxicity, for example, the anthracycline family. Anthracyclines, such as daunomycin, are particularly effective against many types of cancer, but they are prone to cause neutropenia.

H&O Which patient populations are at the highest risk of developing neutropenia?

DD Patients who have the types of cancer that will respond to chemotherapy will receive the most intensive

chemotherapy and therefore will be at the greatest risk of developing neutropenia. We have recently learned that developing neutropenia or having suppression of the bone marrow is concomitant with receiving enough of the drug to affect not only the bone marrow but also the tumor. Patients who get effective therapy receive drugs in doses and durations sufficient to affect the body's cells, both the normal and the cancer cells. On the other hand, if a tumor is not expected to respond to treatment, clinicians generally will not administer the myelotoxic drugs at high dose intensity, except in experimental or clinical trial settings. In this setting, treatment is palliative and so neutropenia is less likely to occur. Thus, the treatment intent, the drugs that are administered, and the dose intensity of treatment are key determinants for the development of neutropenia.

The other way to think about risk is based on the clinical characteristics of the patient. There are subsets of patients who are at greater risk. For example, we have known for a long time that age is an important risk factor, and infections are more severe complications in the elderly than in younger persons.

H&O Is research currently ongoing to identify other characteristics that clinicians can use to assess the risk of neutropenia?

DD From the clinician's perspective, it would be ideal to have a precise diagnosis when the patient is first seen in order to consider treatment as well as a precise estimate of how likely the patient is to have complications from each potential treatment that might be prescribed. Over the last 15 years, a number of researchers have worked to identify risk factors. Important and easily identified risk factors are age, general health or performance status, and comorbidities such as kidney, heart, and lung disease. Diabetes is a particularly important risk factor also. All of these conditions make patients more prone to illness regardless of the specific cancer therapy given to them. Patients with these risk factors and with neutropenia due to suppressed bone marrow are doubly prone to infection.

H&O What were the methods for treating neutropenia before the introduction of granulocyte-colony stimulating factors?

DD For many years after the introduction of chemotherapy, clinicians did not have any treatments for neutropenia or other blood disorders that directly affected blood-cell formation. From the beginning of the use of chemotherapy, however, it was understood that infections occurred when neutrophil counts were low, and antibiotics were a mainstay of treatment. In the 1970s there were many studies on the use of antibiotics to prevent infections. In some studies, massive doses of oral antibiotics were given as prophylactic treatments to cleanse the bacteria from the intestinal tract. This use of large doses of antibiotics occurred in an era when healthcare professionals were very optimistic about antibiotics, the possibility of eliminating infections, and being able to suppress all bacteria. It was expected then that if bacteria became resistant to antibiotics, researchers would discover new antibiotics so that antibiotic resistance would not limit therapy. Looking back, the advances in antibiotic therapy of the 1970s and 1980s were certainly important for the development of modern cancer treatments, but we also gradually learned the limits of this approach to the problem of chemotherapy-induced neutropenia and infections.

The well-known drawback to antibiotic treatment is that additional bacteria emerge as resistant organisms. Infections by organisms that were increasingly unsusceptible to the drugs that were given were the biggest problem. Resistant *Pseudomonas* infections and Gram-negative bacterial infection emerged, followed by resistant fungi and *Staphylococci*, then by resistant organisms of almost any imaginable type. Antibiotic resistance is a very important problem in thinking about cancer treatment. It is made all the more important for cancer patients by the difficulty of finding effective new antibiotics over the last decade. There may be good reason to use antibiotics liberally in cancer patients, but there are also good reasons to be cautious about their use.

H&O What findings led to a change in the approach to treating neutropenia?

DD The discovery that led to a more physiological approach to the problem of neutropenia was a better understanding how blood cells are formed. The key therapeutic discovery was finding the growth factors or stimulating factors for the formation of these cells. The initial discovery of the blood cell growth factors occurred in the 1960s, but it was not until the 1980s that this knowledge was turned into a practical and useful drug through application of methods of modern molecular biology. In the mid-1990s it was established that the growth factors

that stimulate blood-cell formation, and particularly neutrophil formation, could make the marrow recover faster after the insult of chemotherapy. These growth factors could thus be used to prevent infections and to make cancer treatment more widely available and more successful. It was a major advance to have control of the body's own systems for making cells as opposed to what had been the secondary approach of antibiotics alone.

H&O What are the drawbacks of growth factors as therapy for neutropenia?

DD There are not as many drawbacks as might have been expected originally. The production of blood cells is a highly regulated process; growth factors can be used to stimulate production quite effectively. One of the drawbacks is that administration of a growth factor to someone who has a suppressed marrow does not induce an immediate response. Rather, it takes a few days for the response to occur. The marrow must produce the cells, which just takes some time. It would be ideal if the cells were produced immediately, but the body's natural process does not work that quickly. Another drawback is that like all medicines, there are some side effects, such as bone pain and headaches. Fortunately, the colony-stimulating factors and, in general, growth factors stimulating blood-cell formation are relatively well tolerated by most patients. People of all ages, sizes, and diseases can be given these factors. Adverse effects have not proven to be a major problem.

H&O What has been the role of stem cells in creating new treatments for neutropenia?

DD The body's own natural response to neutropenia is to repopulate the system with stem cells and other more mature progenitor cells, which leads to recovery. After cancer chemotherapy or other insults to the marrow, the progenitor cells can proliferate and regenerate the hematopoietic tissues of the marrow, but this takes several days. In most instances we depend on the patient's own endogenous stem cells for this recovery. We have some understanding of this process, but the hormones and all the factors regulating stem cell growth are not yet known.

The colony-stimulating factors are used to stimulate endogenous stem cells and other progenitor cells to recover faster than would otherwise occur. They are also used to promote the release of stem cells from the marrow to permit harvest of stem cells for autologous or allogeneic transplantation when the endogenous supply of stem cells is insufficient or defective. Researchers have been interested in harvesting stem cells, growing them, and making them available for an individual or a population of people.

This process has not yet proven to be successful, but it has attracted much research attention. Currently stem cells have been successfully harvested from and returned to patients to help them recover from high-intensity chemotherapy, but this approach has been applied effectively in treatment to only a fairly narrow group of malignancies up to this point.

H&O What improvements or changes do you foresee in the future with the treatment of neutropenia?

DD I think we are still in the learning phase regarding the dynamics of the drugs used to treat cancer and the supportive measures used to make the treatment tolerable and safe. Researchers are still learning how to define which patients are at greatest risk of developing neutropenia. At the broad level of the healthcare system, we need to be sure that those people who are at risk are treated quickly and treated appropriately. It is important that those who will benefit from modern treatments actually receive them. At another level, we are still learning how to improve care with regard to timing and doses as well as to which drugs and combinations of drugs are best for a given malignancy. I have been impressed by the shifting paradigm to giving chemotherapy at shorter and shorter intervals, known as dose-dense chemotherapy, which is offering hope for more effective or more consistent and effective therapy. Growth factors are the support that allows for dose-dense chemotherapy to be given. Current evidence indicates that dose-dense treatment can both improve the experience of the patients and the clinical outcomes.

H&O What are some of the economic considerations that clinicians have when treating neutropenia?

DD Economic considerations are important; we all need to be cost-conscious in providing health care. All aspects of the health system have become quite expensive for a variety of reasons. A large and growing component of healthcare costs is the medication used to treat cancer, including chemotherapy and the supportive measures like growth factors and other drugs used to make chemotherapy tolerable. In terms of economics, at the present time,

the focus should be on identifying the patients who will benefit most from the most expensive treatments. Another part of this complicated issue is trying to weigh the relative cost in terms of the way drugs are given. For example, it is preferable to administer drugs, including growth factors, on an outpatient basis. Avoiding a hospital stay, which is very expensive, will lower the net cost to society. With regard to neutropenia, a number of researchers have been interested in preventing this side effect through the use of good supportive care, which will lower the net cost to society by decreasing the number of hospitalizations. Often the units that provide care—doctors' offices, clinics, pharmaceutical companies—think in terms of their narrow role, but we need to think of the whole system in terms of the cost and also the benefits to society. I am optimistic that better supportive care will lead to better outcomes as well as reductions in cost.

I often think about medicine from a historical perspective. It is useful to think of how rapidly the changes in the treatment of neutropenia have occurred. The progress in the last decade, for instance, in defining the use of growth factors is remarkable. If we think about the possibility to make that much progress again in the next decade, it will be possible to improve the treatment of cancer patients a great deal and hopefully to manage costs in the process.

Suggested Reading

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