Chemotherapy-induced pain puzzles scientists

By Liz Savage

Some patients describe the pain like walking on shards of glass or hot coals. They complain of a tingling numbness on the palms of their hands and the soles of their feet. Cancer patients rank it near the most intense pain imaginable, 8 or 9 on a 10-point scale. But researchers still don’t understand what causes it or why some people treated with chemotherapy suffer for months or years—while others never experience it at all.

Chemotherapy-induced neuropathy is a loss of sensation in the fingers and toes—a stocking-and-glove distribution—that disrupts normal life for its victims. Patients report having difficulty with simple activities that require a fine sense of touch: picking up a coin, buttoning a shirt, tying shoelaces. Some patients say they can’t walk in the dark because they fall when they can’t see their feet. Oversensitivity to cold transforms an iced beverage into a scalding one, and a walk down the frozen-food aisle at the grocery store becomes unbearable.

The condition affects the sensory nerves that send messages to and from the spinal cord, but researchers don’t know how exactly the nerves are injured or how to treat the pain once it sets in. In many patients the pain begins after the first dose of chemotherapy and can last months, sometimes years, after the treatment has ended. Not all types of chemotherapy cause this pain, but some of the most widely used cancer drugs do—paclitaxel, vincristine, bortezomib, thalidomide, and the platinum-based drugs, like oxaliplatin and cisplatin.

“These are major drugs that are used to treat essentially all the most common cancers that are out there today,” including lung, breast, and colorectal cancer, as well as leukemias and myelomas, said Patrick Dougherty, Ph.D., professor in the department of anesthesiology and pain medicine at the University of Texas M. D. Anderson Cancer Center in Houston.

There have been no epidemiologic studies to determine what percentage of chemotherapy patients is affected. Without a rigorous study of the problem, researchers can draw their impressions from the patients referred to pain centers, where often only the most severe cases are seen.

Ignoring the Problem

Until recently, chemotherapy-related pain was not a major concern for most oncologists and cancer researchers, partly because they had few options for treating this pain though primarily because many patients didn’t live long enough to feel its long-term effects. However, as the ranks of cancer survivors increase, quality-of-life issues have become more important. Yet even now, this common, painful, and often long-lasting condition has caught the attention of only a few cancer researchers.

“It is an important clinical problem that is caught between two disciplines, neither of which fully embraces it,” said Patrick Mantyh, Ph.D., a pain researcher at the University of Minnesota in Minneapolis. Cancer biologists are more concerned with killing the cancer cells than with cancer’s aftermath, and neurobiologists don’t really understand how the cancer drugs work. “This is an interesting and up-and-coming problem because the more aggressively you can treat the tumor, the more likely you’ll have a cure or longer survival,” Mantyh said. But this painful side effect prevents oncologists from giving the optimal dose to kill all the cancer cells and therefore can affect patient survival.

Unfortunately, researchers have more questions than answers about chemotherapy-related pain. The primary question, of course, is what causes it. Several theories are currently being investigated, including the role of faulty microtubules and defective mitochondria in the nerve cells and leaky blood vessels around the nerve cells. Yet for all the pet theories out there, none stands out as the clear answer. The problem is that many of these theories apply to only some of the drugs that cause painful neuropathy. Dougherty and Mantyh predict that, whatever the cause turns out to be, there will be some unifying mechanism for all the pain-inducing chemotherapy drugs.
“It’s a conundrum because most of these agents target different things. They should all be targeting rapidly dividing cells. But the peripheral nerve does not rapidly divide. So why do these compounds, which have such different actions as far as how they kill the cells, bring on this neuropathy?” Mantyh said.

**Treating the Pain**

According to Dougherty’s research so far, about half of his patients’ pain has improved after chemotherapy ends. But for patients whose pain turns into a chronic condition, it doesn’t look like there is currently much hope of reversing the damage. “That’s the sad truth. Patients in that chronic group are showing nerve damage that looks to be permanent,” Dougherty said.

Currently, there are few effective treatment options for chemotherapy-related pain. Medications for depression and seizures have been used, but with limited success. “It’s not always easy to treat neuropathic pain. We seem to do a little better in getting rid of that burning, tingling pain, but we never really get rid of that numbness sensation, which is so troublesome to patients,” said Judy Paice, Ph.D., a cancer pain researcher at Northwestern University.

Since the condition may be irreversible in some patients, researchers are focusing on ways to prevent the pain in the first place. Oncologists know when chemotherapy-induced neuropathic pain will start because they are causing it, unlike other types of neuropathy. “In this particular situation you know when you’re going to give the chemotherapeutic agent, so you could have a therapy on board to protect those sensory neurons before you start it,” Mantyh said.

Gary Bennett, Ph.D., of McGill University in Montreal has had success preventing neuropathic pain in rats with a compound called acetyl-l-carnitine, which is said to have antiaging and neuron-protecting effects. He hopes to get funding to test the drug in humans soon.

If a preventive treatment is discovered, “you’re not only preventing a condition that can cause months or even years of suffering, but it’s the pain and the neuropathy that is limiting the dose of these drugs,” Bennett said. “If we can control the pain and neuropathy, we can give higher doses, kill more tumors, and probably save more lives.”