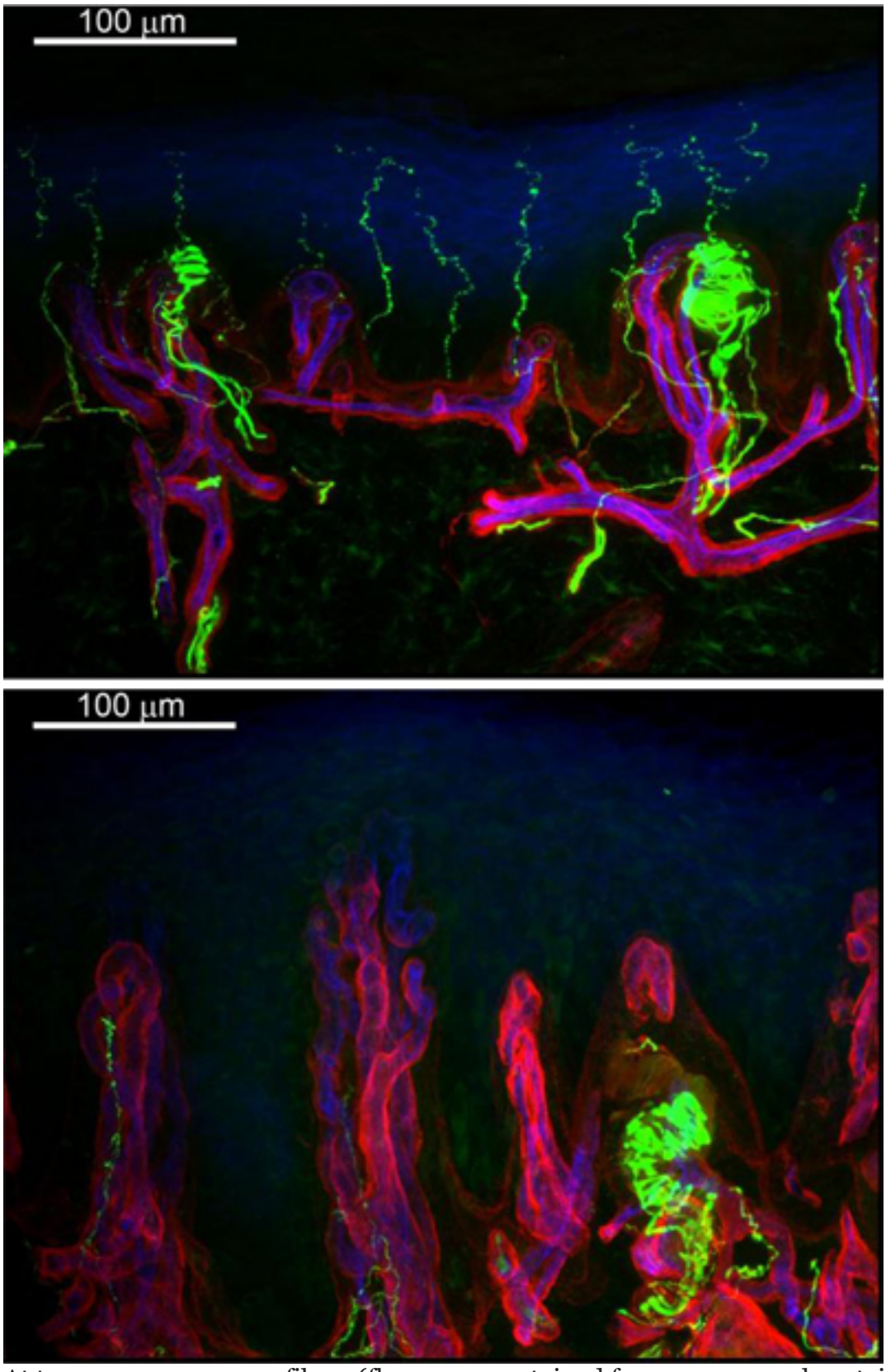
NCI Cancer Bulletin
A Trusted Source for Cancer Research News
February 23, 2010 • Volume 7 / Number 4

A Closer Look

This is the third article in a series of stories related to cancer survivorship. Look for the symbol on the left in an upcoming issue for the next article in the series.

Chemotherapy-induced Peripheral Neuropathy

It usually starts in the hands and/or feet and creeps up the arms and legs. Sometimes it feels like a tingling or numbness. Other times, it's more of a shooting and/or burning pain or sensitivity to temperature. It can include sharp, stabbing pain, and it can make it difficult to perform normal day-to-day tasks like buttoning a shirt, sorting coins in a purse, or walking. An estimated 30 to 40 percent of cancer patients treated with chemotherapy experience these symptoms, a condition called chemotherapy-induced peripheral neuropathy (CIPN).



At top, numerous green fibers (fluorescence stained for pan-neuronal protein PGP9.5) show normal innervation in skin tissue taken from the palm of a healthy

volunteer, where blue stain shows collagen. At bottom, the lack of green shows a loss of innervation to the epidermis of the palm in a patient with chronic chemoneuropathy. (Images courtesy of Dr. Patrick Dougherty at M. D. Anderson Cancer Center, processed in collaboration with the laboratory of Dr. William Kennedy at the University of Minnesota)

CIPN is one of the most common reasons that cancer patients stop their treatment early. (See sidebar for a list of drugs that can cause CIPN.) For some people, the symptoms can be mitigated by lowering the dose of chemotherapy or temporarily stopping it, which diminishes the pain within a few weeks. But, for other patients, the symptoms last beyond their chemotherapy for months, years, or even indefinitely.

"Peripheral neuropathy can be an incredibly debilitating side effect," explained Dr. Ann O'Mara, head of NCI's Palliative Care Program in the Division of Cancer Prevention. "We can't predict who will come down with it or to what degree they will get it. So there are a lot of questions around this issue, in terms of preventing and treating it."

Outside of clinical trials, CIPN symptoms are commonly managed in a manner similar to other types of nerve pain—that is, with a combination of physical therapy, complementary therapies such as massage and acupuncture, and medications that can include steroids, antidepressants, anti-epileptic drugs, and opioids for severe pain. But these therapies have not demonstrated true efficacy for CIPN, and virtually all of the drugs to treat peripheral neuropathy carry side effects of their own.

Life with Neuropathy

Cynthia Chauhan is a patient advocate who is very active in the cancer community. She participates with several boards and committees that advise NCI-sponsored clinical trial groups, including the North Central Cancer Treatment Group and the Southwest Oncology Group, and she is co-chair of the Patient Advocate Working Group for the Translational Breast Cancer Research Consortium. She is also very familiar with the burden of peripheral neuropathy and the shortcomings of current treatments.

A two-time cancer survivor, Ms. Chauhan lives with peripheral neuropathy that arose spontaneously—called idiopathic neuropathy—

nearly 15 years ago. Her symptoms include shooting pains, fiery numbness, and tingling in her hands and feet, as well as a lack of sensitivity to temperatures. Her mother developed chronic CIPN during her treatment for stage IV ovarian cancer and, because of the pain, has terrible difficulty sleeping. “But without the drugs that caused her neuropathy, she would not have survived,” Ms. Chauhan said. “So she uses that knowledge to balance the negative aspects.

“I’m an optimist by nature,” Ms. Chauhan continued. “I like to focus on what I have, rather than what I don’t have, and I can still walk and use my hands—I’m an artist, so my hands are important to me. That I can still use them is very positive.”

She has tried several medications for her neuropathy, and all of the systemic drugs caused unbearable side effects. Today she manages her pain with Lidoderm patches and the practice of guided imagery and meditation, which she says function mostly as distractions for the pain. “Nothing ever stops it. It’s a 24-7 issue with me. I know that drugs work for some people, and if you can find effective medications under the care of a really knowledgeable physician, that’s great,” she said. “But more basic and translational research is critical for those of us who are living with the condition.”

Chemotherapy Drugs Associated with CIPN

- Platinum compounds (cisplatin, carboplatin, oxaliplatin)
- Vincristine
- Taxanes (docetaxel, paclitaxel)
- Epothilones (ixabepilone)
- Bortezomib
- Thalidomide
- Lenalidomide

Understanding the Pain

NCI’s Symptom Management and Health-related Quality of Life Steering Committee, of which Ms. Chauhan is a member, met in Rockville, MD, last year to discuss these issues. This steering committee is one of several that advise NCI as it works to improve the efficiency of clinical trials so that proposed treatment hypotheses can be translated more quickly into new screening, treatment, and prevention options for patients.

What actually causes CIPN, on the cellular and tissue level, is still largely a matter of speculation. There is evidence that nerves can become sensitized because the concentration of salts in the fluid surrounding them changes, or because the channels that use these salts to trigger nerve impulses become dysfunctional. These or other changes may actually damage the structure of nerves. (See image above.)

Because the underlying etiology may vary according to the chemotherapy agent and from patient to patient, more research with animal models is needed, in addition to clinical trials, to try to define the causes of CIPN and identify means to prevent or alleviate it, said Dr. Charles Loprinzi, the Regis Professor of Breast Cancer Research at the Mayo Clinic in Rochester, MN, who chaired the steering committee meeting.

“We need a multi-pronged approach,” he explained. “If we can better understand what causes CIPN in animals and which antidotes might be helpful for preventing and treating it, that doesn’t necessarily mean that [the antidotes] will be exactly the same in humans, but it will allow us the opportunity to screen promising compounds. Ones that successfully alleviate the symptom profiles in animals can be advanced to clinical trials in humans.”

Getting the Right Measures

“I’ve been very lucky not to develop this before now, actually…It’s likely just a side effect of the chemotherapy treatment that I’ve been receiving for the past 10 weeks (Taxol). And that’s why we’re taking a break from chemo this week,” Dr. Susan Niebur wrote in 2007 of her experience with peripheral neuropathy on her blog Toddler Planet, where she documents her experience as a mother and survivor of inflammatory breast cancer.

“Hopefully the week off will allow my system some time to recover and the pain to diminish. Already, my legs are responding more to me (no more wheelchair!) and I can feel my left foot. My right foot and leg, up to the knee, is still tingling and painful to the touch, but I hope that will also resolve in the next few days.” More than 2 years after finishing her chemotherapy, Dr. Niebur still has some residual neuropathy in her right foot and occasionally in her hand, but she

wrote in an e-mail that it's primarily a numbness now, "and a bother more than anything else."

Patient-reported outcomes (PROs) during and after chemotherapy, such as those Dr. Niebur described, will be an important part of future research on CIPN. A tool that was developed by NCI and that is routinely used to record adverse effects from cancer treatment in clinical trials, the CTCAE, "is not adequate to help us fully understand this condition," said Dr. Loprinzi. "As opposed to having a health care provider summarize the symptoms of a patient, it is much preferred to have patients more directly record their symptoms."

PROs commonly include substantially more detailed and accurate information for a variety of symptoms. The steering committee identified several tools, including a 20-item patient questionnaire called the EORTC-QLQ-CIPN20, which appear to better capture this level of information.

Clinical Research Ahead

Several new agents have shown positive effects in pilot studies in patients with CIPN or neuropathy related to diabetes or HIV, and the steering committee has recommended that some of the more promising of these be pursued in larger placebo-controlled randomized clinical trials. Some of these trials are already enrolling patients, while others are still in the planning stages. More information about these trials can be found on NCI's Web site.

For treating the pain associated with CIPN, agents that appear promising include the antidepressants duloxetine (see Featured Clinical Trial in this issue) and venlafaxine, which are both serotonin/norepinephrine-reuptake inhibitors. Another promising agent is a topical compound of the muscle-relaxant baclofen, the antidepressant amitriptyline, and the analgesic ketamine.

For preventing the onset of CIPN, the committee recommended further clinical testing of intravenous calcium and magnesium, which reduced CIPN symptoms by approximately half compared with a placebo in one trial involving patients receiving oxaliplatin; a peptide called glutathione, which is thought to bind to heavy metals and has shown promise in small trials in patients who are treated with

platinum chemotherapies; acetyl-L-carnitine, a substance that was effective in animal models and in patients with diabetes and HIV; and the antioxidant alpha-lipoic acid.

Pharmacogenomic studies will also, it is hoped, help guide the identification of patients who are more or less likely to develop CIPN. One such study is being planned at the Mayo Clinic to determine how a variation in genes that control taxane and carboplatin metabolism may affect a person's risk of getting CIPN.

"I'm a relatively conservative person, in terms of how I practice medicine and research," said Dr. Loprinzi. "But I'm excited about this area. We're just starting to tap it. Over the next few years, as study results become apparent, I'm reasonably confident that one or two, or possibly more, of these agents will be shown to be beneficial for patients."

—Brittany Moya del Pino