Managing Chemotherapy-Induced Neuropathy

Neuromodulation, pharmacological treatments show promise against peripheral neuropathy in cancer patients

By Joe Munch

Characterized by pain and loss of sensation in the hands and feet, chemotherapy-induced peripheral neuropathy (CIPN) can interfere with cancer patients’ treatment and significantly diminish their quality of life. Researchers at The University of Texas MD Anderson Cancer Center are testing new treatments for CIPN, a serious adverse effect of chemotherapy and unfortunately one of the most common.

“Neuropathy is a pretty pervasive problem; it can happen to patients with any type of cancer and be caused by many types of chemotherapy,” said Sarah

Photomicrographs of biopsy specimens from the paws of mice with cisplatin-induced neuropathy treated with control vehicle (left) or the HDAC6 inhibitor ACY-1083 (right) show that ACY-1083 reversed intraepidermal nerve fiber (IENF) loss, an early indicator of axonal pathology. Dashed lines indicate the basement membrane; arrows indicate IENFs crossing the basement membrane. The specimens were stained with antibodies for IENFs (red) and collagen (green). Images courtesy of Drs. Annemieke Kavelaars and Jiacheng Ma.
Prinsloo, Ph.D., an assistant professor in the Department of Palliative, Rehabilitation, and Integrative Medicine. “And there aren’t a lot of effective treatments on the market for it.” Dr. Prinsloo and others are working to change this. In preclinical studies and clinical trials, she and her colleagues are testing pharmacological and noninvasive neuromodulation treatments to control—and perhaps even reverse—CIPN.

**A complex complication**

Chemotherapy induces neuropathy by damaging the nerves that control sensation and sometimes those that control mobility. But why CIPN affects who it does, when it does, is unclear.

“Many factors might contribute to CIPN, including patients’ inherent susceptibility, their genetic makeup, and the amount and duration of their chemotherapy,” said Salahadin Abdi, M.D., Ph.D., a professor in and chair of the Department of Pain Medicine.

Both the onset and duration of CIPN vary among individuals. Some patients experience neuropathy with the first dose of chemotherapy; others may not experience it until late into treatment. Some patients continue to have neuropathy well after treatment has ceased; in others, the neuropathy ends as soon as treatment stops.

What patients with CIPN experience also varies. “It’s classified as a pain syndrome, but patients with neuropathy can have a variety of symptoms. Some patients do have pain, but some just have weird sensations. Sometimes they get super cold; sometimes they are hot. And sometimes it feels like something heavy is sitting on their legs,” Dr. Prinsloo said. “Most of our patients describe numbness, tingling, and complete loss of sensation.”

In some cases, Dr. Prinsloo said, neuropathy in the feet becomes so pronounced that patients can no longer drive because they cannot feel the pressure they are putting on the pedals. Others lose their sense of balance and require the use of a walker.

CIPN is typically treated with anti-depressants, anticonvulsants, and/or analgesics. Topical numbing agents such as lidocaine are sometimes used, and opioids may be employed in cases involving extreme pain. However, none of these options are especially effective, and all have adverse effects.

“Overall, the current medications for treating CIPN are not satisfactory,” Dr. Abdi said. “Other options need to be developed.”

**Neuromodulation offers an alternative**

Given the limitations of currently available pharmaceutical interventions, more physicians and their patients are turning to nonpharmacological means of addressing neuropathy. One area that has shown particular promise is neuromodulation.

“Anything the brain can learn to do—including processing pain—it can learn to do differently,” Dr. Prinsloo said. “Neuromodulation is training the brain to do something different than what it is currently doing using feedback, stimulation, or other nonpharmacological means.”

Neuromodulation-based interventions under investigation at MD Anderson include scrambler therapy, repetitive transcranial magnetic stimulation (rTMS), and neurofeedback.

**Scrambler therapy**

Scrambler therapy prevents damaged nerves from sending their information to the brain to interpret, allowing only normal information through. The result is a reduced perception of pain and improved perception of sensation.

“Patients with CIPN seem to respond well to scrambler therapy, but we do not know why that’s the case.” Dr. Abdi said. “What we do know is that these patients feel better, their pain gets better, they can reduce their medication, and they are able to feel their hands and feet again.”

Scrambler therapy, which has no known adverse effects and can be repeated, is delivered over 10 days in 45-minute sessions. Electrodes are placed around the areas of worst neuropathy to stimulate the C nerve fibers that carry sensory information to the brain. The therapy typically begins to reduce pain within 5–10 minutes and can have long-lasting results.

“The benefit lasts for several months,” Dr. Abdi said. “And when the pain comes back, it’s never as bad as it was prior to treatment.”

Dr. Abdi has used scrambler therapy to treat more than 20 patients with CIPN or neuropathy of other etiologies, including shingles and phantom limb pain. Most of the patients have responded well, but results in patients with CIPN have been particularly promising.

“The results we’re seeing are phenomenal,” Dr. Abdi said. “We looked at 10 patients with CIPN, and they had an average 62.5% reduction in their pain. Nine of those patients reduced their medication. And eight patients had significant improvement in their sensation.”

Dr. Abdi said that he and his colleagues are planning a randomized controlled trial of scrambler therapy, noting that patients will be followed up for at least 6 months to determine the long-term effects of the treatment. In the long run, he said, scrambler therapy may be widely used to treat not only CIPN but also other neuropathic pain syndromes, such as diabetic neuropathy.

“Scrambler therapy is effective for CIPN, and most probably for other types of neuropathy,” Dr. Abdi said. “Given the option to treat my patients with a therapy that does not have adverse effects, it’s an easy decision for me to look into scrambler therapy.”

**“Our recent studies are among the first to show that neuropathy can indeed be reversed with a pharmaceutical.”**

– Dr. Annemieke Kavelaars

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Neurofeedback

Neurofeedback is a form of operant conditioning, which modifies behavior by reinforcing the positive consequences of the preferred behavior. “The brain likes to learn,” Dr. Prinsloo said. “Once it figures out that it will get a reward if it changes its function in a particular site, it will keep trying to earn that reward by doing the new function over and over and over again. Eventually, that becomes the normal function of that part of the brain.”

A course of neurofeedback treatment takes 20 sessions, each lasting less than an hour. Electroencephalography (EEG) sensors are placed on the patient’s scalp at the appropriate locations to track the brain waves in the regions that are active during neuropathy pain episodes. Researchers show the patient a video representation of his or her brain waves while they monitor the patient’s EEG. Every time the patient adjusts his or her brain wave pattern in the way desired, he or she receives positive visual and auditory feedback.

Although patients usually feel relief from symptoms within the first 10 sessions, Dr. Prinsloo said, “If we stop giving them feedback too early, they won’t memorize it. So the goal of those second 10 sessions is memorization. Once we get their neuropathy symptoms to drop, we just repeat the reinforcement until they memorize it.”

In a pilot study of neurofeedback, Dr. Prinsloo and her colleagues randomly assigned 30 CIPN patients with any type of cancer at any stage to a neurofeedback group and another 32 CIPN patients to a wait-list control group (these patients were offered neurofeedback following the study). At the completion of the study, patients in the neurofeedback group had clinically and statistically significant reductions in their CIPN.

Importantly, the neurofeedback group had a 100% completion rate, which Dr. Prinsloo attributes to the patients’ strong desire to obtain relief. She and her colleagues are now investigating neurofeedback for CIPN in a clinical trial for breast cancer patients (No. 2015-0399).

Repetitive transcranial magnetic stimulation

rTMS, which has been around since the 1980s, was first approved by the U.S. Food and Drug Administration to treat depression and more recently approved for language and motor mapping prior to neurosurgery. rTMS has been experimentally shown to be effective for chronic pain syndromes and epilepsy; now, Dr. Prinsloo is investigating the therapy in a clinical trial for colorectal cancer patients with oxaliplatin-induced neuropathy (No. 2016-1134).

“A lot of literature suggests that rTMS works for chronic pain, and some literature suggests that it works for CIPN,” Dr. Prinsloo said. “But no study has looked at it in this population.”

Patients in the trial, which has just begun enrollment, complete rTMS in 10 sessions, each lasting less than an hour. During each session, patients sit in a comfortable chair, and an electromagnetic coil is placed against the side of the head. Targeted magnetic pulses induce electrical currents in the motor strip of the brain to encourage it to change its activity. The treatment has only a few mild adverse effects, such as scalp irritation.

Preclinical work shows promise

Annemieke Kavelaars, Ph.D., a professor in and chair ad interim of the Department of Symptom Research, is using rodent models to investigate several potential pharmaceutical approaches to preventing CIPN, most of which involve protecting the mitochondria in peripheral neurons—cells with a length of up to a meter. For a peripheral neuron to function correctly, it must be able to transport proteins made in the cell body, located in the dorsal root ganglia adjacent to the spinal cord, all the way to the end of the axon in the body’s extremities. This process requires good energy metabolism, which depends on the cell’s mitochondria.

“Chemotherapy damages those energy-producing mitochondria, mainly in the periphery, and that’s why CIPN often starts in the toes, extends to the feet, and then begins to involve hands and, if it gets worse, expands upward to the trunk,” Dr. Kavelaars said. “Because of the damage to those energy factories, the peripheral nerve endings begin to retract from the skin in the hands and feet, and that’s probably contributing to the numbness that people with neuropathy feel.”

Among the agents she and her team have investigated are metformin, the widely used antidiabetic drug, and pifithrin-α (PFT-α), a small compound that inhibits the binding of p53 to mitochondria.

“We have seen that if we protect the mitochondria with either metformin or PFT-α, we can prevent both the pain...
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and the loss of sensation that comes with neuropathy,” Dr. Kavelaars said.

Dr. Kavelaars and her team are also investigating agents that might reverse CIPN. “Many investigators have shown that there are compounds that can help prevent neuropathy—at least in rodent models—but to repair the damage that’s already been done is much more challenging,” she said. “Our recent studies are among the first to show that neuropathy can indeed be reversed with a pharmaceutical.”

One such drug is the novel selective HDAC6 (histone deacetylase 6) inhibitor ACY-1083. “With this drug, we’re seeing more of the healthy mitochondria being transported to the periphery and then regrowth of the damaged nerve endings. The pain and numbness go away,” Dr. Kavelaars said. “It repairs the problem, getting to the cause of the issue.”

In addition to repairing nerve damage, metformin, PFT-µ, and ACY-1083 have been shown to enhance the anticancer effects of other cancer therapies in vitro and even in vivo. In fact, another HDAC6 inhibitor, ricolinostat, which is less selective than ACY-1083, is already being tested for its anticancer-enhancing effects in a clinical trial at MD Anderson (No. 2011-0167, which has completed enrollment).

On the horizon

Even as neuromodulation-based therapies move forward in clinical trials and as new—and existing—agents accumulate promising preclinical data, questions about neuropathy remain.

“We need to understand much more about how neuropathy normally resolves. A significant portion of patients with neuropathy continue to have the problem after they complete chemotherapy, but there’s also a large group whose pain goes away when treatment stops,” Dr. Kavelaars said. “And we don’t know why some people continue to have the problem and others don’t.”

“The answers to these questions, Dr. Kavelaars hopes, will help researchers develop even more effective therapies for CIPN.

“After years of frustration, we’re finally moving toward finding interventions that can truly resolve CIPN,” Dr. Kavelaars said. “There’s real relief for these patients on the horizon.”

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Further Reading


For more information about clinical trials for patients with neuropathy, visit www.clinicaltrials.org and search for study No. 2015-0399 or 2016-1134.

Treating Tobacco

MD Anderson provides phased program plus cessation education, research

By Bryan Tutt

Despite decades of public awareness campaigns about the dangers of tobacco use, smoking continues to be the leading cause of preventable death in the United States, according to the U.S. Centers for Disease Control and Prevention. But researchers at The University of Texas MD Anderson Cancer Center have shown that an integrated program of counseling and proactive pharmacotherapy helps smokers overcome tobacco addiction. Now outreach initiatives are making similar programs available to high-risk populations and sharing smoking cessation tools and expertise with community physicians and other health care professionals.

Spurred by evidence that cancer patients who quit smoking during treatment have better survival outcomes than those who continue to smoke, MD Anderson faculty members established the Tobacco Treatment Program in 2006. The program is available at no charge to all MD Anderson cancer patients as well as employees and their families.

The program’s success has led to several ongoing clinical trials to further test its interventions and eventually disseminate the program to a broader population. Furthermore, the faculty and staff are using videoconferencing technology and specialized training courses to help community health care professionals establish similar smoking cessation programs.

Tobacco Treatment Program

MD Anderson’s Tobacco Treatment Program integrates behavioral counseling, pharmacotherapy, and—when needed—psychological or psychiatric care. The result is a program that is tailored to help each patient overcome the unique obstacles to quitting smoking that he or she faces. “We leave no stone unturned,” said Maher Karam-
Hage, M.D., a professor in the Departments of Behavioral Science and Psychiatry and the associate medical director of the Tobacco Treatment Program. He added that although almost all participants in the program are cigarette smokers, the program also works for users of other tobacco products.

The first step in the program is an interview with a behavioral counselor who is a certified tobacco treatment specialist with training in motivational counseling. “The counselor explains to the patient what quitting involves, how to prepare, and what situations are likely to cause cravings,” said Vance Rabius, Ph.D., an instructor in the Department of Behavioral Science and the research director of the Tobacco Treatment Program. “The counselor works with the patient to develop strategies to deal with relapses, cravings, and withdrawal.”

A week or two before the patient plans to stop smoking, he or she begins pharmacotherapy. Typically, a combination of nicotine replacement therapies (e.g., patches with lozenges) or a combination of bupropion and nicotine replacement is used because such combinations are less expensive than varenicline and have equivalent success rates. However, pharmacotherapy may later be adjusted to fit the patient’s needs.

“We take a proactive approach to pharmacotherapy,” Dr. Karam-Hage said. “If the patient is not making progress or has trouble quitting, we change the medication from nicotine replacement to bupropion or varenicline and vice versa. We don’t wait for the treatment to fail.”

If the patient remains tobacco free after 3 months of pharmacotherapy, he or she receives another 3-month supply of bupropion or varenicline if one of those drugs was used. Dr. Karam-Hage believes the extended course of pharmacotherapy, which is longer than that prescribed by many physicians, improves the patient’s chances of long-term abstinence from smoking. If the patient does not remain tobacco free during the course of pharmacotherapy, the treatment team develops alternative cessation strategies and discusses these with the patient.

For the first 8–12 weeks, the patient meets with a behavioral counselor. All behavioral counseling sessions can be done in person, over the phone, or by videoconference. After the last of these sessions, the patient is followed up by phone every 3 months for a year.

Patients in the program also receive psychiatric evaluation and care if needed. “Psychological counseling and psychiatric treatment help deal with issues like other addictions, depression, or anxiety,” Dr. Rabius said. “The fact that we offer psychological and psychiatric treatment in addition to behavioral counseling—plus the way we approach pharmacotherapy—makes our program unique.”

The program also offers a phone-only option in which patients receive behavioral counseling but not pharmacotherapy or psychiatric care.

The results from the Tobacco Treatment Program’s 10-year experience were published last year. Among patients surveyed 9 months after their

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quit date, 47% reported that they had remained abstinent from smoking. “The success rate for smokers who try to quit on their own is about 3%,” said Dr. Karam-Hage, the first author of the report. “It’s not even comparable.”

Outreach

Building on the success of the Tobacco Treatment Program, MD Anderson faculty members are working to give a broader population of smokers the tools they need to quit. The faculty members are also providing education and support to help physicians and other community health care providers implement smoking cessation programs.

The faculty members identified participants in MD Anderson’s low-dose computed tomography lung cancer screening program as a population that could benefit from smoking cessation intervention because the eligibility requirements for such screening include a smoking history of at least 30 pack-years (see “House Call: Lung Cancer Screening,” OncoLog, March 2017). For participants in the lung cancer screening program who are current smokers, a clinical trial of three smoking cessation strategies is now available (No. 2016-0626).

Participants in the trial are randomly assigned to one of three groups. Participants in the first group are referred to the state quitline for counseling by a tobacco cessation counselor and receive nicotine replacement therapy in the form of a patch. Participants in the second group are referred to the state quitline and receive bupropion, varenicline, or nicotine replacement therapy as prescribed by the screening radiologists. Those in the third group are referred to the Tobacco Treatment Program. The trial, led by Paul Cinciripini, Ph.D., a professor in and chair of the Department of Behavioral Science, will compare 6-month smoking abstinence rates among the three groups.

The researchers anticipate that the third group, which receives comprehensive treatment through the Tobacco Treatment Program, will have the highest quit rates.

Other clinical trials are bringing the Tobacco Treatment Program to new populations while evaluating the efficacy of the interventions used in the program. For example, two ongoing trials led by Dr. Cinciripini are comparing the efficacy of varenicline to that of nicotine replacement therapy in participants who also receive behavioral counseling. Both trials (Nos. 2014-0207 and 2014-0213) are currently enrolling smokers age 18–75 years.

Another population that could benefit from a smoking cessation program is patients treated at publicly funded local mental health authorities (LMAHs) for bipolar disorder, chronic depression, and psychotic disorders. “The smoking rate is 60%–70% in this population,” said Jan Blalock, Ph.D., an associate professor in the Department of Behavioral Science. “These patients are dying up to 25 years younger than people in the general population, predominantly from smoking-related illnesses.”

To help practitioners at LMAHs throughout Texas provide smoking cessation services, Dr. Blalock and her colleagues in MD Anderson’s EndToBacco initiative and Tobacco Treatment Program as well as at Rice University developed a videoconference format called Project TEACH (Tobacco Education And Cessation in the Health System). Project TEACH is an extension of Project ECHO (Extension for Community Healthcare Outcomes), a worldwide program in which specialists at academic medical centers share information and discuss cases with providers in underserved communities. Project TEACH began 2 years ago to provide telementoring for clinicians and counselors at LMAHs in Texas, and the program has recently been expanded to include community health care practitioners throughout the country.

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Smoking-Related Cancers

Cancer risks from tobacco are not limited to the lungs, but quitting reduces these risks

Most people are aware that smoking is the most common cause of lung cancer, but fewer may know that smoking causes many other types of cancer as well. In fact, according to the U.S. Centers for Disease Control and Prevention (CDC), cigarette smoking either directly causes or contributes to 30% of all cancer-related deaths in the United States—including almost half the deaths from 12 types of cancer.

Risks to smokers

Of the 700–800 naturally occurring chemicals in tobacco smoke, at least 69 can cause cancer. Because these dangerous chemicals travel through the bloodstream to all parts of the body, smoking-related cancer can occur almost anywhere in the body. For example, smoking may double the risk of one type of skin cancer, squamous cell carcinoma.

Head and neck cancers have long been linked with the use of tobacco, especially in the tissues of the mouth and throat that inhaled tobacco smoke has to pass through. According to the CDC, 85% of head and neck cancers are linked to the use of cigarettes or other tobacco products such as cigars or chewing tobacco. And alcohol use multiplies the risk of head and neck cancers in smokers.

Tobacco use is also the principal cause of bladder cancer in the Western world, according to the World Health Organization (WHO). Smoking accounts for 50% of bladder cancers in men and 35% of bladder cancers in women. The WHO estimates that the risk of bladder cancer is two to three times higher for smokers than for nonsmokers, while the U.S. National Cancer Institute estimates that the risk for smokers is four times higher.

Cigarette smoking also increases the risks for acute myeloid leukemia and for cancers of the kidney, pancreas, stomach, uterus, cervix, ovary, colon, and rectum, according to the American Cancer Society.

Risks to nonsmokers

Exposure to secondhand smoke causes cancer, cardiovascular disease, and other diseases as well as premature death in nonsmoking adults and children. The U.S. Environmental Protection Agency, the U.S. National Toxicology Program, the U.S. Surgeon General, and the International Agency for Research on Cancer have all classified secondhand smoke as a known cancer-causing agent.

Secondhand smoke has been proven to cause lung cancer, and some studies suggest that secondhand smoke causes other cancers as well. Specifically, studies have linked secondhand smoke to cancers of the throat in adults and to lymphoma, leukemia, and brain tumors in children.

Benefits of quitting

Many factors contribute to a smoker’s risk of cancer, including the number of years the person has smoked, the number of cigarettes smoked each day, and the age at which the person began smoking.

The good news is that quitting smoking can significantly decrease a smoker’s chances of developing or dying from cancer. For people who already have cancer, quitting smoking reduces the risks of disease recurrence and of developing a second form of cancer. For cancer patients undergoing surgery, chemotherapy, or other treatments, quitting smoking improves the body’s ability to heal and to respond to therapy. Quitting smoking also lowers these patients’ risk of developing pneumonia or respiratory failure.

Smokers of any age can benefit from quitting smoking. Those who quit before their mid-30s can lower their health risks to the same level as those of nonsmokers within a few years. And those who quit smoking at age 50 years reduce their risk of dying prematurely by 50%. Studies have also shown that even people who quit smoking at 60 years or older live longer than those who continue to smoke.

It takes a few years after quitting for ex-smokers’ cancer risk to decline, but the benefit increases the longer a person does not smoke. There are also immediate health benefits to quitting smoking, such as improvements in lung function, a lowering of blood pressure and heart rate, improved circulation, and less coughing.

For smokers in almost any age group or health condition, stopping smoking has major health benefits.

FOR MORE INFORMATION

• Talk to your physician
• Visit MD Anderson’s Tobacco Treatment Program at www.mdanderson.org/quitnow or call 713-792-QUIT
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Each Project TEACH videoconference connects 15–20 participants with a multidisciplinary team of MD Anderson experts. Part of each session is devoted to didactic information about evidence-based practices in pharmacotherapy or counseling for smoking cessation, and part is an interactive discussion about current cases. There is no cost to participants.

Also provided free of charge is an online course about pharmacological options and counseling to help patients quit smoking. The course is available to physicians, physician assistants, nurse practitioners, counseling clinicians, and other health care professionals for continuing education or continuing medical education (CME) credit.

MD Anderson also hosts an in-person course through which licensed professional counselors, social workers, and other professionals can become certified tobacco treatment specialists. The 4-day course, which is accredited by the Council of Tobacco Treatment Training Programs, is held 2 or 3 times each year. A registration fee is required.

Those who complete the tobacco treatment specialist certification course are encouraged to join the Project TEACH videoconferences. “Practitioners who want to provide good, evidence-based tobacco cessation services may benefit from intensive training followed by the opportunity to reinforce their knowledge and discuss cases with our experts and the other partners in the videoconferences,” Dr. Blalock said.

Dr. Rabius encourages physicians to use these resources and offer smoking cessation services to their patients who smoke. “At a minimum, doctors can refer their patients to a quitline and get them started on pharmacotherapy,” he said. “But I would advise community physicians to look into our CME and videoconference programs to improve their understanding of smoking cessation.”

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