New NCCN Guidelines for Peripheral Neuropathy

BY ED SUSMAN

HOLLYWOOD, Fla.—A new treatment algorithm presented here at the National Comprehensive Cancer Network's 19th Annual Conference provides strategies to help control peripheral neuropathy.

Susan G. Urba, MD, a member of the NCCN Survivorship Guideline Committee and Professor of Internal Medicine, at the University of Michigan Comprehensive Cancer Center, said that the condition is not only painful and upsets quality of life, but is one of the main reasons cancer patients either have to change or stop their treatments.

"Neuropathic pain can last months, years, or indefinitely," she said in outlining the expanded survivorship guidelines. "The survivorship guidelines are the 'mother ship.' We have divided them into the major categories that survivors have to deal with: Pain is one of those categories, and peripheral neuropathy is a small subset of that.

"A picture is worth a thousand words," she continued. "I have had numerous patients describe to me that peripheral neuropathy in the feet is like standing on a cactus, walking on tacks, or walking on shards of glass. The prevalence is 20 to 40 percent of individuals undergoing certain types of chemotherapy. For a lot of patients who finish their chemotherapy, the neuropathy does resolve, but there are a fair number of patients for whom the condition continues indefinitely."

In presenting the guidelines, SUSAN G. URBA, MD, noted that the pain of peripheral neuropathy is one of the main reasons that cancer patients either have to change or stop their treatments.

> "In pain management, a team effort is necessary to comprehensively assess and treat the impact of pain."

The following drugs are all associated with varying degrees of peripheral neuropathy, she said:

- Platins, such as cisplatin and particularly, oxaliplatin;
- Taxanes such as paclitaxel and docetaxel;
- Vincristine;
- Bortezomib;
- Lenalidomide;
- Ixabepilone; and
- Thalidomide

"I realize that I see the worst of the worst in my symptom management clinic, and there probably are a lot of patients out there who are doing just fine. Patients on Velcade [bortezomib] have a fair amount of neuropathy that we really have to fight through."

continued on page 9

PERIPHERAL NEUROPATHY

Continued from page 8

Start with Antidepressants or Anticonvulsants

In interactive audience participation, Urba asked what the first treatment for a patient who presented with suspected chemotherapy-related peripheral neuropathy should be, and most of the audience selected either antidepressants or anticonvulsant therapy. "I think that is correct," she said.

She noted that the guidelines for overall cancer treatment suggest that doctors screen patients for pain, and even if a patient has no pain at one visit, doctors are advised to rescreen patients at subsequent sessions. If the screening reveals peripheral pain, then the guidelines give choices for treatment.

The guidelines call for the use of adjuvant analgesics, including the use of antidepressants, anticonvulsants, and corticosteroids, sometimes in conjunction with opiates or separately. A lot of this is extrapolated from studies on diabetic neuropathy, she said. "It is considered strong enough support that we have often incorporated this into the guidelines as a good rationale.

> "For many patients who finish their chemotherapy, the neuropathy does resolve, but there are still patients for whom the condition continues indefinitely."

"Antidepressants and anticonvulsants are first-line adjuvant analgesics for the treatment of cancer-related neuropathic pain, the principles of adjuvant analgesic use states. These drugs can be helpful for patients whose pain is only partially responsive to opioids.

"Analgesia is not dependent upon antidepressant activity," Urba continued. "The analgesic dose may be less than what is used for depression, yet the lower analgesic dose may work more quickly to treat pain than the antidepressant can treat depression."

She noted that in a review of 31 studies, about one third of patients did receive relief of pain with tricyclic antidepressants. Most of the studies were testing the antidepressants against diabetic neuropathy or post-herpetic neuralgia. However, 20 percent of patients withdrew for adverse events such as drowsiness, blurred vision, and urinary retention.

"If you start at a low dose and titrate slowly every three to five days, then sometimes a patient can tolerate it better," Urba said. "Nortriptyline is the number one antidepressant we use because it has the fewest side effects. The treatment with these drugs can help those who have difficulty sleeping, can ease a bit of their depression, and reduce neuropathic pain."

Serotonin-Norepinephrine Reuptake Inhibitors

Another group of drugs, the serotonin-norepinephrine reuptake inhibitors, also appear to be effective, she noted. Studies with duloxetine indicate that the treatment relieves pain without disruption of activities of daily living.

"We don't often think of venlafaxine for neuropathic pain," Urba said, pointing, though, to one trial of oxaliplatin-related neuropathic pain, in which about a third of patients achieved complete pain relief and more than two thirds had at least 50 percent pain relief, which was significantly more than with placebo. The patients on venlafaxine also had fewer Grade 3 adverse events.

Either duloxetine or venlafaxine can be used as another type of antidepressant, Urba said, explaining that the serotonin-norepinephrine reuptake inhibitors are a bit more effective than the selective serotonin reuptake inhibitors such as citalopram or paroxetine.

For breast cancer patients on tamoxifen, these latter drugs may also have interactions. The selective serotonin reuptake inhibitors can prevent tamoxifen from converting to its active form and should be avoided among the 20 to 40 percent of women with breast cancer who are taking tamoxifen and antidepressants, Urba said.

The guidelines also recommend the use of anticonvulsants for control of neuropathic pain. "Gabapentin is the one most of us think about. Even though we start the guidelines mentioning antidepressants, there is no reason not to start with gabapentin. A lot of patients end up on both if one of the agents doesn't give full relief."

She said that the treatment algorithm for the use of gabapentin was influenced by two clinical trials in diabetic neuropathy, which demonstrated superiority in reducing pain with gabapentin over placebo, even among patients whose pain was only partially controlled by opioids.

Pregabalin also appears to control neuropathic pain as well as improve sleep disturbance when compared with placebo—"These types of drugs can be very helpful," she said.

Opiates represent another option for treatment, and doctors are also advised to discuss cognitive behavior therapy and psychosocial support for these patients.

If a patient has refractory pain, the guidelines suggest considering referral to pain-management services, an interventional specialist, a physical therapist, physical medicine, and/or rehabilitation. The algorithm also suggests that doctors consider dorsal column stimulation.

Topical Therapies

There are also topical therapies for patients who experience peripheral neuropathy, Urba noted. For example, lidocaine patch 5% showed effectiveness against pain at two and four hours and at four and seven hours. "It was significantly better at all time points, so that is a good option," she said. "In my experience, some people say that the patch saves the day for them, while others say it didn't touch the pain."

Another topical agent for neuropathic pain is capsaicin—"perfectly reasonable to think about," Urba said. The agent blocks pain signaling to the brain, but has a short-lived burning sensation when first applied. "Some patients don't like that and won't use it again," she said. Clinical studies with capsaicin have demonstrated significant benefit over placebo, she added.

An 8% capsaicin patch also affords relief of pain, but it comes with some costs to convenience. The patch was tested in post-herpetic neuralgia and consists of a 60-minute application that is performed in the clinic. Patients do not apply it themselves. It is used with a topical analgesic. Gloves have to be worn in the application process. It has been shown to provide relief for as long as 12 weeks.

Diclofenac gel 1% applied once a day is concentrated in the dermis, so it has less gastrointestinal side effects than systemic delivery does, Urba said. Results of a clinical trial in breakthrough pain associated with knee osteoarthritis have not yet been reported, but it was decided nonetheless to include that

continued on page 10

> Coping skills—breathing exercises, distraction techniques, guided imagery, and hypnosis—can be used in conjunction with appropriate analgesia to enhance a sense of personal control and refocus energy on optimizing quality of life."

NCCN Speaker Doesn't Let Plane Crash Stop Her Presentation

BY ED SUSMAN

HOLLYWOOD, Fla.—Before Crystal Denlinger, MD, of Fox Chase Cancer Center delivered a talk at the National Comprehensive Cancer Network Conference here, she first helped lead the evacuation of a jetliner that crashed on takeoff at Philadelphia International Airport.

"It wasn't a big deal," she said in an interview. "It was probably more traumatic seeing the pictures of it later than being a part of it."

The routine trip from Philadelphia on US Airways Flight 1702 ended abruptly when the front nose tire blew out and the landing gear collapsed.

"I was sitting in the middle exit row seat, so the women next to me opened the door," Denlinger recalled. "I stepped around to the other side and she was holding the door and I said, 'Okay, I'll take that.' I stepped out and took the door with me out of the plane and stuck it on the wing. You are supposed to open the door and then get out, so that's what we did."

She said she had been mildly nervous about sitting in the emergency exit row, so "this time I actually read the card and looked at how I was supposed to open the window if necessary.

CRYSTAL DENLINGER, MD

"We had weaved a little bit before we started to fly, and then we bounced and got up in the air again

"Then we came back down and skidded to a nice stop, and they told us to sit for a while. The flight attendants asked, 'Is everyone okay? Is anyone hurt?' No one was. Then there started to be some smoke, and there were people yelling, and finally the first officer said, 'Evacuate.' And then it got a little chaotic.

"The flight attendants didn't help us that much," she said. "They didn't tell us to open the window. But everybody got out okay, and then immediately after we got out people started taking pictures. There was more on social media within five minutes after the crash than I would think humanly possible. Frankly, as soon as I knew the plane was not going to explode and I was a safe distance away, I turned around and took a picture, too, and posted it on Facebook."

While waiting on the tarmac in the wintry afternoon, the passengers gathered together to help each other. "It was cold, but it was a good feeling to see the passengers huddle together. Not many of us had brought coats off the plane. We figured out who was in T-shirts or light dress shirts and huddled around them. We were all sharing phone chargers so we could call our families. Then I got on a plane at midnight and got to the meeting at 3 am. I had a job to do, so I got on the plane."

She also was scheduled to present a poster study at the NCCN meeting, but left that on the plane when she was evacuated. She eventually got it from the plane later, though, hung it up before giving her talk, speaking at a Point-Counterpoint session on "Challenges of Communicating with Patients about Optimal Post-treatment Surveillance—Patient Expectations versus Scientific Evidence."

PERIPHERAL NEUROPATHY

Continued from page 9

"Antidepressants and anticonvulsants are first-line adjuvant analgesics for cancer-related neuropathic pain, and can be helpful for patients whose pain is only partially responsive to opioids."

as a mention in the guidelines, she explained.

Another topical option is the combination of ketamine 1% and amitriptyline 2% cream. In a small study of 28 patients, five patients achieved a 50 percent or greater reduction in pain and one patient was pain free. At one year, patients overall had a reduction in pain of 37 percent. Some payers, though, she noted, will not cover the $50 a month cost of preparing the cream through compounding pharmacies.

Corticosteroids, although often used for patients with pain crises, are rarely used in long-term therapy, Urba said. Because corticosteroids have a long-half life, they can be dosed once daily. They are, though, associated with myopathy, gastric irritation, and adrenal suppression

Psychosocial Support

The guidelines also note, she said, that psychosocial support is also an integral part of care in addition to use of specific medications—specifically, clinicians should "educate the patient and the family/caregiver that in pain management a team effort is necessary to comprehensively assess and treat the impact of pain. Members of the team may include an oncologist, nurse, pain specialist, palliative care clinician, physiatrist, neurologist, psychologist, social worker, psychiatrist, physical therapist, and spiritual counselor."

The statement also suggests that teaching of coping skills be used in conjunction with appropriate analgesia to enhance a sense of personal control and refocus energy on optimizing quality of life—for example, breathing exercises, distraction techniques, guided imagery, and hypnosis.

The guidelines also include an algorithm that addresses opioid tolerance, she said. The main guidance includes use of the lowest dose possible, with functionality as the endpoint for measuring outcome. If there is no improvement in function, the opioid dose should be tapered slowly.

In addition, she said, patients who are experiencing refractory pain should be referred to a pain specialist. Use of transcutaneous electrical nerve stimulation, which has been successful in treating diabetic neuropathy, can also be considered for cancer patients.