Abstract
The NCCN Clinical Practice Guidelines in Oncology for Survivorship include a new section on cancer-associated cognitive impairment and an expanded section on adult cancer pain that more completely addresses chemotherapy-induced peripheral neuropathy. These additions to the guidelines are the result of increasing awareness that long-term cancer survivors struggle with many late effects. Both the assessment and the management of cognitive impairment still lack a strong evidence-based foundation. The management of peripheral neuropathy, including the use of antidepressants and opioids, often in combination, is backed by data primarily derived from clinical trials performed for various types of peripheral neuropathy. (*J Natl Compr Canc Netw* 2014;12:825–827)

NCCN has expanded the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Survivorship to include a section on cancer-associated cognitive impairment and to include chemotherapy-induced peripheral neuropathy as a component of the section on adult cancer pain.

The inaugural guidelines for cognitive impairment were presented at the NCCN 19th Annual Conference by Elizabeth Kvale, MD, Director of Supportive Care and Survivorship, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, and Susan G. Urba, MD, Professor, Medical Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, described the new section on peripheral neuropathy.

Cognitive Impairment in the NCCN Guidelines
Dr. Kvale said that increasing recognition of cognitive impairment and a concern for patients led to the development of the cognitive function guideline for cancer survivors.

“Chemotherapy-associated cognitive impairment is a common experience for cancer survivors and it has been underrecognized. The guidelines are an important validation of our patients’ symptomatic experience, and they will allow clinicians to take a structured approach to evaluating it and to supporting patients who have this problem,” Dr. Kvale said.

For a subset of patients, cancer and its treatment disrupt “normal” cognitive function, and these changes have important implications for quality of life and function, she said.

The guidelines acknowledge this, and indicate that these changes have been modestly correlated with testing; 16 of 21 longitudinal studies in breast cancer showed evidence of cancer-associated cognitive impairment, particularly verbal ability and speed of processing. In a 2012 meta-analysis of 17 breast cancer trials, deficits in cognitive functioning were observed in patients treated with chemotherapy relative to controls or to prechemotherapy baseline in the domains of verbal ability (P<.01) and visuospatial ability (P<.01). ①
The most reliable figure is that 20% to 30% of patients report some cognitive impairment, which is transient for most, but persists in a "subset of vulnerable patients," she said.

Dr. Kvale said a Google search for “chemobrain + blog,” in preparation for her presentation produced 591,000 results. “Patients think about this a lot,” she emphasized. The condition, however, is still not well understood. “It is probably a real phenomenon, as anatomic and functional imaging studies show that it’s real, but we lack evidence to clarify the causes and what we should do about it. We aren’t seeking a single cause, as we believe there are multifactorial elements to the phenomenon [Figure 1],” she said. “Longitudinal studies are needed to evaluate cognitive function before and after chemotherapy.”

Assessment and Management of Chemobrain
Neuropsychologic testing can help “sort out” the condition, Dr. Kvale noted, especially in elderly patients who may have dementia. Neuroimaging, on the other hand, is generally not helpful clinically; however, an expanding evidence base is now suggesting that structural and functional changes underlie the experience, she added.

Patients who present with symptoms of cognitive impairment should also be screened for potentially reversible contributing factors, especially depression. Currently, there is no effective brief screening tool, and available instruments lack adequate sensitivity for subtle declines in cognitive performance.

Limited evidence is available to guide management of the condition, especially for cancers other than breast, Dr. Kvale indicated.

“Current management strategies are patient-centered, supportive, and nonspecific,” she said, and the NCCN Guidelines list some interventions that can be helpful. “Reassurance and watchful waiting are not inappropriate for many patients, because many issues resolve on their own.”

Chemotherapy-Induced Peripheral Neuropathy
Currently, perhaps more can be offered to the 20% to 40% of patients who experience peripheral neuropathy as a result of chemotherapy, a sizeable proportion

Figure 1 Proposed mechanisms for “chemobrain.”
Abbreviation: CNS, central nervous system.
of whom have persistent pain. “Peripheral neuropathy has been part of the cancer pain guidelines for years, but we are now focusing more on the long-term cancer survivor, and some of these patients have persistent pain,” Dr. Urba said.

First-line treatment of peripheral neuropathy is antidepressants (especially duloxetine) and anticonvulsants (gabapentin and pregabalin). These are often effective on their own, but can be combined with opioids when pain is severe or refractory, Dr. Urba said.

In placebo-controlled trials, approximately one-third of patients experienced at least moderate relief from tricyclic antidepressants, but side effects can be intolerable to some. The effectiveness of serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine is also supported by data, such as the recent trial of duloxetine in which pain severity was significantly improved after 5 weeks versus placebo \((P<.001)\), as were daily function \((P=.01)\) and quality of life \((P=.03)\).

Anticonvulsants can be helpful, although some patients find them too sedating. Gabapentin is started at 100 to 300 mg nightly, increasing to 900 or even up to 3600 mg daily in divided doses. Pregabalin is started at 50 mg 3 times a day, increasing to 100 mg 3 times day. Lower doses should be given to patients who are elderly and those with renal dysfunction.

If opioids are necessary, the lowest dose should be used, and for long-term use, clinicians may consider establishing a pain treatment agreement, Dr. Urba said. “Clinicians don’t worry about a patient being on gabapentin for years, but they can be uncomfortable prescribing opioids long-term.”

Other interventions recommended by NCCN include topical agents, such as 5% lidocaine patch or compounded creams (usually best when combined with an antidepressant, anticonvulsant, or opioid).

Psychosocial support of patients experiencing peripheral neuropathy is important, she emphasized. “They may be on lifelong medication, and they should learn coping skills,” she said. Because of the multidimensional nature of treatment-induced neuropathy, she recommends a “team effort” to provide patient support.

References
