Managing Breast Cancer–Related Symptoms

BY BRUCE JANCIN
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SAN ANTONIO — The flip side of the impressive decline in breast cancer mortality during the last several decades is the unprecedented number of survivors with tough-to-control chronic symptoms caused by the disease or its aggressive therapy, Dr. Charles L. Loprinzi said at the San Antonio Breast Cancer Symposium.

He focused on evidence-based therapies of five of the most common and problematic breast cancer survivorship issues: vaginal dryness, fatigue, chemotherapy-induced neuropathy, diminished libido, and hot flashes.

Vaginal dryness. Pilocarpine (Salagen) shows enough promise that Dr. Loprinzi and colleagues have embarked on an ongoing randomized, double-blind, placebo-controlled trial of the oral drug at 5 mg once daily or b.i.d. in 192 women treated for breast cancer. Results should be available next year.

The impetus for the study was an anecdotal report a few years ago of marked clinical improvement in cyclophosphamide-induced vaginal dryness in four patients, along with a separate earlier report of significantly decreased vaginal dryness as a secondary outcome measure in a phase III trial of pilocarpine for oral and ocular dryness in patients with Sjögren's syndrome (Arch. Intern. Med. 1999;159:174-81). The drug is approved for that indication as well as for dry mouth caused by head and neck radiation therapy.

Estrogen therapy is effective for vaginal dryness and is worthwhile in some severely affected women, but there is concern that it could promote breast cancer recurrence. That concern extends to vaginal estrogens as well.

"All of the vaginal agents, in my mind, do lead to systemic levels of estrogen in some patients," said Dr. Loprinzi, professor of medicine and chair of oncology at the Mayo Clinic, Rochester, Minn.

Nonestrogenic vaginal lubricants are "somewhat effective," but are clearly inferior to estrogen in comparative studies, he added.

Fatigue. This is a major complaint for cancer patients across the full spectrum of disease, from those on adjuvant chemotherapy to patients with advanced, incurable cancer. Exercise is the intervention with the strongest evidence base.

"Exercise is the answer, not more rest," Dr. Loprinzi emphasized.

Modafinil, donepezil, L-carnitine, and methylphenidate have been looked at in pilot studies, but more work is needed before any of them can be recommended for cancer-related fatigue.

Similarly, Dr. Loprinzi and coworkers were encouraged by the results of their pilot 8-week, double-blind dose-finding study of American ginseng, in which roughly 25% of cancer patients on 1,000 or 2,000 mg/day of ginseng reported their fatigue was moderately to very much better, compared with 10% on placebo.

'Exercise is the answer, not more rest,' for patients experiencing fatigue after chemotherapy.

DR. LOPRINZI

"The evidence isn't there to recommend ginseng for use at this time, but we're excited about it. The toxicity profile looked very favorable. We're about to start a larger placebo-controlled trial," the oncologist said.

Chemotherapy-induced neuropathy. Gabapentin is widely prescribed for this problem. However, the sole rigorous study to date—a multicenter, placebo-controlled, double-blind, crossover trial conducted by Dr. Loprinzi and colleagues in the North Central Cancer Treatment Group (NCCTG)—failed to demonstrate any benefit (Cancer 2007;110:2110-8).

Vitamin E (alpha-tocopherol) at a dose of 400 mg/day was reported to protect against cisplatin-induced peripheral neuropathy and ototoxicity in an interim analysis of a 50-patient randomized, placebo-controlled study presented at last year's American Society of Clinical Oncology meeting. The NCCTG has an ongoing randomized trial, also comparing vitamin E at 400 mg/day and placebo. Until the results are in, Dr. Loprinzi urged caution in using vitamin E for prevention of chemotherapy-induced neuropathy.

"We haven't proved that it's helpful, No. 1, and also there are some data suggesting that vitamin E can get in the way of cytotoxic therapy, particularly radiation therapy for the head and neck area. Maybe that will also apply to chemotherapy. We need to sort all this out," he said.

Low libido. Sexual counseling is the only thing that can be recommended. Transdermal testosterone cream proved ineffective in a double-blind, randomized, placebo-controlled crossover trial conducted by Dr. Loprinzi and the NCCTG (J. Natl. Cancer Inst. 2007; 99:672-9).

Testosterone did improve low libido in several prior studies in women without cancer. The most likely explanation for the disparate results lies in the fact that all participants in those studies were either premenopausal or on estrogen replacement therapy; in contrast, the cancer patients weren't receiving estrogen, he noted.

Hot flashes. Effective nonhormonal therapies are available. Dr. Loprinzi and his colleagues showed in a randomized, double-blind, placebo-controlled trial that venlafaxine at 37.5 or 75 mg/day reduced hot flash scores by 40% and 60%, respectively, from baseline (Lancet 2000;356:2059-63).

In a subsequent double-blind, placebo-controlled crossover trial, they demonstrated that fluoxetine at 20 mg/day also was effective in reducing hot flashes in women with a history of breast cancer (J. Clin. Oncol. 2002;20:1578-83), although it appears to be less so than venlafaxine.

Paroxetine at 20 mg/day appears to be roughly as effective as venlafaxine at reducing hot flashes, based upon randomized controlled studies by other investigators. Sertraline at 50 and 100 mg/day doesn't seem to work as well as do the other antidepressants.

Tamoxifen is metabolized by cytochrome P450 2D6 to a key active metabolite, endoxifen, which is believed to be responsible for the selective estrogen receptor modulator's efficacy in preventing breast cancer. Coadministration of paroxetine and tamoxifen has been reported to result in a significant decrease in plasma endoxifen levels (J. Natl. Cancer Inst. 2003;95:1758-64). In contrast, venlafaxine didn't reduce endoxifen levels in another study (Clin. Pharmacol. Ther. 2006;80:61-74) . ■

Zoledronic Acid Infusions Cut Treatment-Related Bone Loss

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — Zoledronic acid infusions proved dramatically effective in preventing the pronounced bone loss that accompanies combination estrogen-reducing adjuvant endocrine therapy in premenopausal breast cancer patients, according to an update from a major Austrian clinical trial.

Indeed, the number of such patients who needed to be treated (NNT) with the third-generation bisphosphonate to prevent one additional case of osteopenia at 3 years was just 4.5 in the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12), Dr. Michael Gnant reported at the San Antonio Breast Cancer Symposium.

Treatment-induced bone loss was particularly severe in participants who received goserelin plus the aromatase inhibitor anastrozole (Arimidex) without zoledronic acid (Zometa). By the time adjuvant therapy ended after 3 years, they averaged a 14% reduction from baseline in lumbar spine bone mineral density (BMD). Their BMD showed only partial recovery at 5 years—2 years after the conclusion of adjuvant therapy—with an 8% decrease from baseline.

In contrast, those patients randomized to a 15-minute, 4-mg infusion of zoledronic acid every 6 months for 3 years averaged a 3.1% increase over baseline in lumbar spine BMD at 5 years, said Dr. Gnant, professor of surgery at the Medical University of Vienna.

Patients on goserelin and anastrozole alone averaged a 14% reduction from baseline in lumbar spine BMD.

DR. GNANT

Prevention of bone loss in breast cancer patients treated with hormonal therapy is at present an off-label application for zoledronic acid.

The bisphosphonate's approved indications are treatment of patients with multiple myeloma, documented bone metastases from solid tumors, and hypercalcemia of malignancy.

The ABCSG-12 study involved 1,801 premenopausal women with stage I or stage II endocrine-responsive breast cancer and fewer than 10 positive lymph nodes. Dr. Gnant presented the 5-year results of the bone protection substudy, in which 404 patients on 3 years of goserelin were randomized to concurrent tamoxifen or anastrozole; half of those patients were randomized to twice-yearly zoledronic acid.

After 5 years, fewer than 50% of patients on goserelin plus anastrozole alone had normal bone health; the rest had osteopenia or osteoporosis. In contrast, roughly 70% of patients on anastrozole and zoledronic acid had normal bone health both at baseline and follow-up.

The NNT for zoledronic acid to prevent one case of osteoporosis at 3 years was 6.2, climbing to 15.5 at 5 years.

Expressed in terms of T scores, patients on goserelin and anastrozole alone averaged a 1.3–standard deviation loss at 3 years at the lumbar spine, with a half–standard deviation recovery by 5 years.

The BMD loss with goserelin plus tamoxifen alone, while less extensive, was still problematic: an average 9% decrease from baseline at 3 years and a 4.5% loss from baseline at 5 years. With zoledronic acid, however, BMD increased by 1% from baseline at 3 years and by 5.2% at 5 years. The NNT to prevent one case of osteopenia at 3 years in tamoxifen-treated patients was seven.

Dr. Gnant pronounced as excellent the safety and tolerability of zoledronic acid in this study. Bone pain, arthralgia, and fever were the only side effects that significantly increased in the bisphosphonate-treated group. There were three cases of osteonecrosis or osteomyelitis of the jaw, all in the zoledronic acid group. Dr. Gnant reported no relevant conflicts of interest.

"We believe that prevention of treatment-induced bone loss should be considered for premenopausal breast cancer patients receiving estrogen-reducing adjuvant therapies," he concluded.

Audience member Dr. Mark Graham of the University of North Carolina at Chapel Hill congratulated Dr. Gnant on what he hailed as "certainly one of the most useful clinical studies presented in the last 5 years." ■