Managing Breast Cancer–Related Symptoms

**BY BRUCE JANCIN**

**Denver Bureau**

**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 cytoplasmic-pamide-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.

Modeled on 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.

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, with 10% on placebo.

“The evidence isn’t there to recommend ginseng for use at this time, but we’reизатор about it. The toxicity profile looked very favorable. We’re able 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. That will also apply to chemotherapy. We need to sort all this out,” he said.

**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 was effective in 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 with 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 Grant 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 results of their pilot study, 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. Grant, professor of surgery at the Medical University of Vienna.

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

The bisphosphonate’s approved indications are treatment of patients with multiple myeloma, documented bone metastases from solid tumors, and hypercalcaemia of malignancy. The trial included 1,801 premenopausal women with stage I or II breast cancer randomized to goserelin and placebo with or without zoledronic acid every 6 months for 3 years.

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

**DR. GNANT**

Dr. Grant 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 osteopenia at 3 years in tamoxifen-treated patients was seven.

Dr. Grant 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. Grant reported no relevant conflicts of interest.

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

Audience member Dr. Mark Graham of the University of North Carolina at Chapel Hill congratulated Dr. Grant on what he hailed as “certainly one of the most useful clinical studies presented in the last 3 years.”