Zoledronic Acid Slows Bone Loss in Breast Ca Tx

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — Zoledronic acid prevents the profound loss in bone mineral density that often occurs with combined adjuvant endocrine therapy in premenopausal breast cancer patients, Michael Gnant, M.D., reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Based on new data from the Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG-12), all premenopausal breast cancer patients receiving combination adjuvant therapy with a luteinizing hormone–releasing hormone analogue, such as goserelin, plus either tamoxifen or an aromatase inhibitor, should undergo annual bone mineral density (BMD) testing. Those showing a treatment-related decline should be considered for intravenous zoledronic acid (Zometa) administered once every 6 months, said Dr. Gnant, professor of surgery at the University of Vienna.

In clinical practice, the aromatase inhibitors increasingly are replacing tamoxifen because they provide a greater reduction in recurrence and less risk of endometrial cancer and thromboembolic events. The price has been the greater risk of osteoporosis and fractures associated with aromatase inhibitor use. But prophylactic zoledronic acid appears to erase that downside.

Although it is widely appreciated that postmenopausal breast cancer patients face increased risk of accelerated bone loss, the osseous impact of cancer therapies in premenopausal breast cancer patients was much less clear before ABCSG-12. The primary end point in the 1,315-patient phase III Austrian study will be relapse-free survival, which awaits longer follow-up.

In San Antonio, Dr. Gnant reported on a secondary study end point—change in BMD—in a 401-patient subset.

The ABCSG-12 trial is a four-part study that randomized patients to 3 years of adjuvant goserelin plus either tamoxifen or anastrozole, with or without 3 years of zoledronic acid given at 4 mg IV every 6 months.

After 3 years of goserelin and tamoxifen without zoledronic acid, BMD at the lumbar spine fell an average of 11.6%, compared with baseline. In patients receiving goserelin plus anastrozole but not zoledronic acid, it fell 17.4%. However, patients on either combination who received the potent intravenous bisphosphonate had no significant change in BMD, he said.

In a separate study, Adam Brufsky, M.D., presented preliminary 6-month results from Z-FAST, a 5-year multicenter U.S. trial in which 415 postmenopausal women with early-stage hormone receptor–positive breast cancer receiving adjuvant letrozole (Femara) were randomized to zoledronic acid administered every 6 months either up front or beginning 1 year after the start of the aromatase inhibitor.

BMD at the lumbar spine and hip increased in patients who got zoledronic acid up front and decreased in those assigned to delayed bisphosphonate therapy. Biochemical markers of bone turnover decreased from baseline to 6 months in the up-front zoledronic acid group, while increasing or remaining unchanged in the delayed-treatment arm.

These early findings suggest administration of zoledronic acid from the onset of adjuvant aromatase inhibitor therapy may prevent cancer therapy–induced bone loss in postmenopausal women. However, longer-term follow-up is needed to fully define the effects of zoledronic acid in this population. The Novartis-sponsored Z-FAST trial is scheduled for 5 years of follow-up, said Dr. Brufsky of the University of Pittsburgh. Zoledronic acid is more expensive than pamidronate (Aredia), the other intravenous bisphosphonate, but its infusion time is only 15 minutes, compared with 2 hours or more for pamidronate, and there are some data to suggest zoledronic acid is more effective.

The osseous impact of breast cancer therapies in premenopausal patients was much less clear before ABCSG-12.

DR. GNANT

Zoledronic acid does not yet have an indication from the Food and Drug Administration for use in the setting of adjuvant breast cancer therapy, however, many oncologists will continue to follow the American Society of Clinical Oncology's recent guidelines. Those call for increased diligence in screening breast cancer patients for bone loss, advising them on the importance of calcium and vitamin D supplementation and bone-healthy lifestyle measures, and the early use of the clearly less potent oral bisphosphonates in women who show cancer treatment–related decline in BMD. ■

Teens Rapidly Recover BMD Lost on DMPA Contraceptive

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

Adolescent women who use the injectable contraceptive depot medroxyprogesterone acetate lose bone mineral density each year they are on the drug but appear to rapidly recover that loss when the drug is withdrawn, results of a prospective study suggest.

"The potential loss of bone density is one consideration of the many that go into a women's choice of contraceptive method," said Delia Scholes, Ph.D., of the Center for Health Studies, Seattle, and her associates.

Dr. Scholes and her associates prospectively examined BMD in a cohort of 170 females aged 14-18. A total of 80 participants were using DMPA, and 90 were not. The DMPA-exposed teens were significantly more likely to be current smokers, to have been pregnant, have reached earlier menarche, and have a higher body mass index and body fat percentage (Arch. Pediatr. Adolesc. Med. 2005;159:139-44).

During the study, 61 of the DMPA users discontinued the contraceptive, affording the opportunity to observe any subsequent changes in BMD.

The DMPA-exposed subjects were receiving the standard dose of 150 mg every 3 months. About 30% of them had received only 1 injection, 31% had received 2 or 3 injections, 21% had received 4-7 injections, and 18% had received at least 18 injections. In the comparison group, 19% were using oral contraceptives at baseline.

BMD was measured at the hip, spine, and whole body every 6 months for 24-36 months. After adjustment the DMPA users had lost significantly more BMD at the hip (–1.81% vs. –0.19%) and spine (–0.97% vs. 1.32%), compared with nonusers. Both groups gained BMD when the whole body was measured, but the DMPA users gained significantly less than the nonusers (0.73% vs 0.88%). New users lost bone faster than continuous users. After 24 months, new users showed a –6.09% change at the hip, compared with –2.05% in continuous users and –0.92% in nonusers.

Among the 61 subjects who discontinued DMPA during the study, BMD increased. Their annualized adjusted mean change in BMD was 1.34% for hip, 2.86% for spine, and 3.56% for the whole body. There was no significant difference in BMD between nonusers and those who discontinued DMPA 18 months earlier.

The injection is highly effective in preventing pregnancy and may help reduce compliance problems, the researchers said.

In 2004, the Food and Drug Administration issued a black box warning for DMPA stating that prolonged use of the drug could result in significant loss of bone density, that the loss is greater the longer the drug is administered, and that bone density loss may not be completely reversible after discontinuing the drug. ■

Teriparatide Speeds Healing of Fractures

COLORADO SPRINGS — The anabolic bone-forming agent teriparatide (Forteo) is winning anecdotal raves for augmentation of fracture healing in both nonosteoporotic and osteoporotic patients.

"This is a very exciting metabolic therapy. My experience so far really does show that it works," Thomas P. Knecht, M.D., declared at a meeting of the Colorado chapter of the American College of Physicians.

Acceleration of fracture healing is an off-label use of teriparatide, the N-terminal 34-amino-acid chain of human parathyroid hormone. Teriparatide's approved indications are for treatment of postmenopausal osteoporotic women at high fracture risk, and for increasing bone mass in osteoporotic men at elevated fracture risk.

The evidence for augmentation of fracture healing comes from multiple favorable animal studies as well as anecdotal clinical experiences that are consistent with the animal findings, explained Dr. Knecht, an endocrinologist at the University of Utah, Salt Lake City.

He offered two illustrative cases from his own practice, both involving middle-aged recreational athletes eager for a rapid return to sports.

One was a 48-year-old man with type 1 diabetes and normal bone mineral density test scores who became severely hypoglycemic, lost consciousness, and fell, fracturing his right tibia and fibula in multiple places. Surgeons placed a metal rod knee to ankle.

The bone pain quickly became nonlimiting after Dr. Knecht placed him on teriparatide.

He began long-distance running 3 months post surgery, and downhill skiing a week after that.

"My assessment of this patient's response was that placebo can't do that. Nobody placebos their way through a fracture like that one. So you have to say the healing was dramatic and the pain response was dramatic," he observed.

Another patient was a 38-year-old woman, also with normal T scores on dual x-ray absorptiometry bone mineral density testing, who fell while training for a half-marathon and fractured her great toe. The break involved the metatarsophalangeal joint.

Yet her fracture pain resolved after a single week on teriparatide. Six weeks later she completed her half-marathon.

While both these patients had good bone mineral density, Dr. Knecht said he has regularly seen the same sort of results—"not only a dramatic pain response, but an absolutely striking metabolic response"—in patients he has placed on teriparatide to augment healing of osteoporotic fractures.

While daily subcutaneous injections of teriparatide are typically given for 2 years in patients taking the agent for the approved indications, 6 months of therapy appears to be "more than adequate" for fracture healing per se because the healing occurs so quickly, he continued.

This is a high-cost drug. Its off-label use to accelerate fracture healing requires a highly motivated patient willing to take on a substantial out-of-pocket expense, according to Dr. Knecht, who is on the speakers' bureau for Eli Lilly & Co., which markets teriparatide.

—Bruce Jancin