# Biomarker Signals Bone Metastases in Breast Ca

BY NANCY WALSH
*New York Bureau*

TORONTO — Increased urinary excretion of a biomarker of bone resorption signals the presence and extent of bone metastases in breast cancer patients, Dr. Diana J. Leeming said at a world congress on osteoporosis.

Technetium-99 ($^{99}$Tc) bone scintigraphy remains the standard method of detecting skeletal metastases in cancer patients. However, this approach is not suitable for close, frequent monitoring because of significant radiation exposure, Dr. Leeming said.

She and her colleagues previously investigated a number of biomarkers to determine if their presence correlated with the number and extent of bone metastases (Cancer Epidemiol. Biomarkers Prev. 2006;15:32-8). Among these were the resorption markers ααCTX and ββCTX; bone-specific alkaline phosphatase (a bone-formation marker); and markers of osteoclastogenesis, such as osteoprotegerin.

They determined that ααCTX—which is the nonisomerized form of the C-telopeptide of collagen type I—correlated most closely with the Soloway score quantification of bone metastases. "We have shown that, for a Soloway score of 1, indicating fewer than six metastases, ααCTX is approximately 200% increased. With a Soloway score of 3, when more than 20 metastases are present, ααCTX is elevated more than 600%," said Dr. Leeming of Nordic Bioscience A/S, Herlev, Denmark.

The current study included 90 patients with newly diagnosed breast cancer; 45 had bone metastases verified by $^{99}$Tc scintigraphy or other imaging studies. The concentration of CTX fragments was measured in morning urine using ELISA (amyloid-β peptide enzyme-linked immunosorbent assay). There were no differences in age or body mass index between patients with and without metastases.

Mean ααCTX in patients without metastases was 0.39 mcg/mmol, a level that correlates with that seen in normal, age-matched healthy controls. For the group with metastases, however, the level was significantly higher, at 1.23 mcg/mmol, according to Dr. Leeming. Analysis also revealed that the presence of one, two, and three metastases was associated with increases of 38%, 57%, and 81% in ααCTX, respectively.

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"This suggests that ααCTX may be sufficiently sensitive to detect the first bone metastasis," she said. Histologic analysis of bone biopsy specimens using cytokeratin and tartrate-resistant acid phosphatase (TRACP) staining confirmed the localized presence of ααCTX and an increased number of osteoclasts near the tumor. The production of CTX is part of a vicious cycle, in which breast cancer cells induce RANK-L (receptor activator of nuclear factor kappa β ligand) in osteoblasts by a number of cytokines, Dr. Leeming explained. This in turn increases the number and survival of osteoclasts, and when osteoclasts resorb bone they release proteins and growth factors from the matrix, further activating cancer cells.

"This high bone remodeling could explain the release of increased levels of ααCTX," said Dr. Leeming at the meeting, which was sponsored by the International Osteoporosis Foundation. ■

# *Patients With GI Intolerance Prefer Injectable Ibandronate*

BY NANCY WALSH
*New York Bureau*

TORONTO — Women with postmenopausal osteoporosis who had previously discontinued oral bisphosphonate therapy because of gastrointestinal intolerance preferred an intravenous, every-3-month regimen of ibandronate over a monthly oral regimen, Dr. E. Michael Lewiecki reported at a world congress on osteoporosis.

Adherence was addressed in a 12-month, open-label multicenter study that included 542 patients with osteoporosis or osteopenia who had stopped daily or weekly treatment with oral alendronate or risedronate because of perceived or actual symptoms such as heartburn and acid reflux. All received supplemental vitamin D (400 IU/day) and elemental calcium (1,000 mg/day).

Patients were given the choice of oral ibandronate, 150 mg once monthly, or 3 mg intravenously every 3 months. The intravenous injection takes 15-30 seconds to complete. A total of 396 (73%) of patients chose the intravenous regimen, while 146 (27%) chose the oral route.

They were permitted to switch treatment groups once during the study if they experienced adverse effects, he noted.

Severity and frequency of gastrointestinal symptoms and other side effects were evaluated with surveys administered at baseline and at months 1, 4, 7, and 10.

Available data indicate that adherence to both regimens at 6 months was high, at 94.5%. Actual duration of study medication intake divided by maximum duration of intake and a threshold of 75% or more was used to define adherence, according to Dr. Lewiecki of New Mexico Clinical Research and Osteoporosis Center, Albuquerque.

Among patients receiving the oral drug, adherence was 87.7%, while adherence was 94.9% among those receiving the intravenous formulation, Dr. Lewiecki wrote in a poster session; the meeting was sponsored by the International Osteoporosis Foundation.

Among patients who chose the intravenous route of administration, 147 (37.1%) had a history of fracture as an adult, compared with 36 (24.7%) of those who chose the oral drug.

Thus far, 26 patients have switched their route of administration. Eleven switched from oral to intravenous ibandronate because of gastrointestinal intolerance, while 15 switched from intravenous to oral for reasons including influenzalike symptoms and injection-site reactions.

By month 4, 28.1% and 36.6% of patients on the oral and intravenous drugs, respectively, reported improvements in gastrointestinal tolerance compared with baseline.

"Based on these findings, it appears that patients who had previously discontinued weekly or daily oral bisphosphonates because of gastrointestinal intolerance prefer intravenous dosing, and that patients with a previous fracture are even more likely to do so than patients without a previous fracture," Dr. Lewiecki concluded. ■

# Calcium Supplements Provide Modest Bone Increase in JRA

BY CHRISTINE KILGORE
*Contributing Writer*

Daily supplementation with calcium and vitamin D boosted bone mineral density by a small but statistically significant amount in children with juvenile rheumatoid arthritis who were not being treated with corticosteroids, according to findings from a randomized, double-blind, placebo-controlled trial.

"Since peak bone mass is achieved no later than the end of the second decade of life, efforts to increase bone mineralization in children with JRA must be started at an early age," said Dr. Daniel J. Lovell of the Cincinnati Children's Hospital Medical Center and his associates.

The investigators were cautious in their interpretation of the findings, however, concluding that the increase in bone mineral density (BMD) was not enough to provide "strong support" for the use of routine calcium supplementation in children with JRA who are not taking corticosteroids. The 198 children in the study had not received corticosteroids for at least 3 months prior to the 24-month study, and many had normal or nearly normal baseline BMD.

The children, aged 6-18 years (mean age of 12 years), had had JRA for a mean of 6 years. They were randomized to receive two daily oral tablets—either an oral supplement of 1,000 mg calcium (taken as 2,500 mg calcium carbonate) and a tablet containing 400 IU of vitamin D, or a matched placebo tablet and 400 IU of vitamin D, for 24 months.

They underwent dual x-ray absorptiometry at baseline and then every 6 months, and their adherence to the treatment regimen was regularly assessed. They were permitted to continue taking nonsteroidal anti-inflammatory drugs and antirheumatic medications. Patients in both treatment groups had similar levels of physical activity and dietary intake of calcium at baseline and throughout the study.

At baseline, the mean total body BMD was 0.89 gm/cm$^2$ among patients randomized to receive calcium, and 0.87 gm/cm$^2$ among those randomized to receive placebo. At 24 months, the total body BMD had increased to 0.95 gm/cm$^2$ in the calcium group (a 6.7% increase) and 0.92 gm/cm$^2$ (a 5.8% increase) in the placebo group.

Similarly, patients treated with calcium had a higher lumbar spine BMD—and a higher percentage change in lumbar spine BMD—than did control patients. But, "as expected, all patients demonstrated increases in (total body BMD) and lumbar spine BMD," Dr. Lovell and his associates said (Arthritis Rheum. 2006;54:2235-42).

When the investigators adjusted for baseline differences in BMD and relevant "outcome effect modifiers," they found significantly higher total body and mean lumbar spine BMD in patients who received calcium.

The increased rate of bone mineralization in the calcium group was seen during the first 18 months only, however. For the last 6 months of the study, BMD increased at a similar rate in both groups, "suggesting that a threshold for the biologic effect of Ca supplementation had been reached," the investigators said.

And although statistically significant, the increases in BMD were surprisingly small, they said. Based on an earlier small, open study that showed increased bone mineralization with calcium supplementation, the investigators had projected a 10% greater increase in total body BMD in calcium-treated patients.

The "modest response . . . may be a reflection of the pathogenic mechanisms of JRA-associated osteopenia," they wrote. "The potency of [inflammatory cytokines] to mediate BMD, and their systemic overproduction in autoimmune diseases such as JRA may be difficult to overcome with oral calcium treatment alone."

Adherence to the supplementation regimen was "very good overall" in the study—much higher than in other studies—which means that "the effect of calcium supplementation, when used as part of routine clinical care … may therefore be less than the effect seen [here]," they said.

The study did not address the role of calcium supplementation in patients with JRA who require treatment with corticosteroids or who already have significantly decreased BMD, they noted. ■