Denosumab's Mixed Results in Cancer Trials

BY PATRICE WENDLING

BERLIN — Denosumab was superior to zoledronic acid in the treatment of bone metastases in advanced breast cancer, but not so in the treatment of multiple myeloma or select solid tumors, according to data from two phase III trials.

The trials—Denosumab 136 and Denosumab 244—were presented at the joint congress of the European Cancer Organization and the European Society for Medical Oncology.

Compared with zoledronic acid, denosumab delayed time to first on-study SRE, but not significantly.

DR. HENRY

Dr. Alison Stopeck, who led the Denosumab 136 study in breast cancer, told reporters at an Amgen-sponsored press briefing that denosumab is clearly a first-line therapy.

In the Denosumab 136 trial, denosumab was superior to zoledronic acid in delaying the time to a first on-study skeletal-related event (SRE), defined as fracture, spinal cord compression, or radiation or surgery to bone. In all, 2,046 advanced breast cancer patients with bone metastases were studied. The median time to first SRE was not reached for denosumab, and was 26.5 months for zoledronic acid, said Dr. Stopeck, director of the clinical breast cancer program at the University of Arizona, Tucson.

Denosumab also significantly delayed the time to first and subsequent SREs, with 474 events reported in the denosumab arm and 608 in the zoledronic acid arm.

Renal failure occurred significantly more often in patients treated with zoledronic acid than denosumab (25 vs. 2 patients), as did acute renal failure (7 vs. 1 patient).

In the Denosumab 244 trial, the median time to first on-study SRE was 20.6 months for denosumab and 16.3 months for zoledronic acid among 1,776 advanced cancer patients with multiple myeloma or solid tumors, excluding breast and prostate cancer, a nonsignificant difference, reported lead author Dr. David Henry.

There were 392 first and subsequent SREs with denosumab vs. 436 such events with zoledronic acid, but again the difference was not significant, said Dr. Henry, a hematologist/oncologist at the Pennsylvania Hospital in Philadelphia.

Renal failure occurred in 25 of the 878 patients in the zoledronic acid group and in 20 of the 878 patients in the denosumab group. Acute renal failure was seen in 16 vs. 11 patients, respectively.

The Food and Drug Administration is expected to announce an approval decision on denosumab for the treatment of osteoporosis soon.

Both trials were supported by Amgen. Dr. Stopeck disclosed financial relationships with Novartis and Amgen. Dr. Henry disclosed relationships with Amgen, Ortho-Biotech Products LP, and Watson Pharmaceuticals Inc. ■

CVD Diagnosis Raises Hip Fracture Risk 'Considerably'

BY MARY ANN MOON

The risk for hip fracture rises steeply after patients have a major cardiovascular event, most likely because of genetic factors common to both vascular and bone disorders, a Swedish study has shown.

In a population-based study of nearly 32,000 twins in Sweden, the rate of hip fracture rose "considerably" in both men and women following any of several cardiovascular disease (CVD) diagnoses. Most of that increase appeared to be explained "by genes or by early environmental sharing" rather than individual lifestyle habits or other individual-specific environmental factors, said Dr. Ulf Sennerby of Uppsala (Sweden) University and associates.

'We advocate that individuals with a recent diagnosis of CVD should have their future fracture risk evaluated with clinical risk factors and bone scans.'

"We advocate that individuals with a recent diagnosis of CVD should have their future fracture risk evaluated with clinical risk factors and bone scans," such as the recently established 10-year probability using the FRAX (the World Health Organization's fracture risk assessment tool) algorithm, they noted.

The researchers used data from an extensive twin registry to examine the relation between CVD events and hip fracture. It included twin pairs who were born between 1914 and 1944 and were subsequently followed from the age of 50 years. It identified 31,936 pairs in which one twin developed CVD or hip fracture by Dec. 31, 2005.

The crude absolute rate of hip fractures in the cohort was 12.6 per 1,000 person-years after a diagnosis of heart failure, 12.6 per 1,000 person-years after a stroke, 6.6 per 1,000 person-years after a diagnosis of peripheral atherosclerosis, and 5.2 per 1,000 person-years after a diagnosis of ischemic heart disease, compared with 1.2 per 1,000 person-years for those without a CVD diagnosis.

All CVD diagnoses were associated with a higher risk of hip fracture independent of other CVD diagnoses and other comorbidities, the investigators said (JAMA 2009;302:1666-73).

The association was stronger in women than in men, but it was significant in both sexes.

Co-twins of subjects who had CVD also were at increased risk of sustaining hip fracture during follow-up, even if they had not had a cardiovascular event. For example, co-twins of subjects who had heart failure were at fourfold higher risk of fracturing a hip, compared with co-twins of subjects with no CVD.

The risk of hip fracture was higher in identical twins who had such "pseudoexposure" and lower in fraternal twins, indicating that an as-yet unidentified genetic factor predisposes people to both vascular and bone disorders, Dr. Sennerby and his associates said.

A subgroup of 24,598 subjects participated in telephone interviews to assess anthropomorphic, lifestyle, and medical factors. The inclusion of these factors into the data analysis did not materially change the results.

It is possible that "specific genes involved in cellular mechanisms shared by the vasculature and bone" may eventually explain this association between CVD and hip fracture, the authors wrote. "Matrix proteins supporting bone, vessel walls, and the myocardium [may] be of special relevance.

Dr. Sennerby reported no financial conflicts of interest. ■

Age Paradox in Bisphosphonate Users

Calcification *from page 1*

lower prevalence of cardiovascular calcification at nearly all anatomic sites assessed.

For example, aortic valve calcification was 33% less common in the older bisphosphonate users than in nonusers in multivariate analyses adjusted for age, BMI, ethnicity, socioeconomic variables, cardiovascular risk factors, statins, and hormone therapy. Aortic valve ring calcification was 35% less common in older user, mitral annulus calcification was 46% less common, and thoracic aorta calcification was 32% less prevalent.

The only anatomic site where calcification wasn't significantly less common in older bisphosphonate users than nonusers was in the coronary arteries, where the adjusted 10% reduction in favor of the bisphosphonate users fell short of statistical significance, Dr. Elmariah continued.

The story was very different in women under 65. Younger bisphosphonate users were an adjusted 4-fold more likely to have aortic valve calcification than were nonusers, 1.9-fold more likely to have aortic valve ring calcification, and 2.4-fold more likely to have calcification of the mitral annulus.

These younger users also had 2.2-fold and 1.2-fold increased rates of calcification of the thoracic aorta and coronary arteries, respectively, all statistically significant differences.

When the women were grouped in 10-year age subsets, a gradual reduction in the adjusted prevalence of cardiovascular calcification accompanied increasing age among bisphosphonate users.

The increased prevalence of cardiovascular calcification in younger bisphosphonate users came as a surprise in light of the known pharmacologic actions of the nitrogen-containing bisphosphonates, said Dr. Elmariah. He noted that the bisphosphonates have several statin-like effects stemming from their inhibition of farnesyl pyrophosphate synthase, an enzyme downstream from HMG-CoA reductase in the mevalonate pathway.

The study was funded by the New York Academy of Medicine, the GlaxoSmithKline Research & Education Foundation, and the National Heart, Lung, and Blood Institute. ■

Anticonvulsants Linked With Low Bone Mass

BANGKOK, THAILAND — Long-term antiepileptic drug therapy is associated with worsening bone health in premenopausal women.

Dr. Rungsan Chaisewikul of Siriraj Hospital, Bangkok, included 50 women with epilepsy and 51 matched controls in his study, presented during the meeting's poster session. All the women were premenopausal, with a mean age of 33 years. Patients had been receiving antiepileptic drugs (AEDs) for at least 3 years. Most (62%) were taking more than one drug, and most (84%) were taking an enzyme-inducing AED. All participants had bone mineral density (BMD) measured at the lumbar spine, left femur, and left radius.

Compared with controls, patients had significantly lower T-scores at the femoral neck (0.30 vs. –0.08). BMD at the lumbar spine was lower, but not significantly lower, in patients than in controls, as was BMD at the radius.

With measurements at the femoral neck and lumbar spine significantly more patients than controls were rated as having osteopenia and osteoporosis. More patients than controls also were rated as osteopenic or osteoporotic when considering the radius measurement, although the difference was not statistically significant.

—Michele G. Sullivan