Early Zoledronic Acid Beats Late for AI Bone Loss

BY BRUCE JANCIN
Denver Bureau

San Antonio — Up-front administration of zoledronic acid in postmenopausal women taking an aromatase inhibitor to reduce their risk of recurrent breast cancer is significantly more effective at preventing bone loss than a strategy of delayed initiation of zoledronic acid, according to 36-month data from Z-FAST, the Zometa-Femara Adjuvant Synergy Trial.

This Z-FAST finding casts into question the current guideline-recommended strategy of reserving bisphosphonate therapy for the subset of breast cancer patients who experience marked loss of bone mineral density (BMD) or a fracture while on an aromatase inhibitor (AI). A routine of prophylactic bisphosphonates from the onset of AI therapy appears to be a better way to go, Dr. Adam Brufsky asserted at the annual San Antonio Breast Cancer Symposium.

On the other hand, Z-FAST didn't show a significant difference in fracture rates with up-front—as compared with delayed—initiation of zoledronic acid (Zometa), and fractures are the key end point in clinical practice, audience members countered.

Z-FAST was an open-label trial that involved 602 postmenopausal women with early-stage, hormone-receptor–positive breast cancer at 94 U.S. and Canadian sites who were placed on 5 years of adjuvant therapy with the AI letrozole (Femara), along with calcium and vitamin D supplements. The women were randomized to up-front intravenous zoledronic acid at 4 mg twice yearly or to delayed initiation of the third-generation bisphosphonate.

Women in the delayed-initiation group were placed on zoledronic acid if their lumbar spine or total hip BMD T score fell below –2.0 standard deviations or if they experienced a clinical fracture or an asymptomatic spinal fracture detected on a mandatory x-ray, which was part of the study protocol. Through 36 months, 20% of patients in the delayed-initiation group qualified.

The primary study end point was change in lumbar spine BMD, compared with baseline. The up-front therapy group showed a mean 3.72% increase; the delayed group showed a 2.95% decrease, for a highly significant absolute 6.7% difference favoring up-front therapy. When patients in the delayed-initiation group who had been placed on zoledronic acid were excluded, this difference climbed to 8.2%. Markers of bone turnover were effectively suppressed in the up-front therapy group only.

The fracture rate was 5.7% in the up-front group and 6.3% in the delayed zoledronic acid group, a nonsignificant difference. However, Z-FAST wasn't powered to detect a difference in fractures, stressed Dr. Brufsky of the University of Pittsburgh.

The rate of recurrent breast cancer was 3.5% in the up-front zoledronic acid arm and 6.9% in the delayed group. "These numbers are fairly small—9 versus 16 patients—and did not achieve statistical significance. And these data are only exploratory. But they are rather interesting," he observed.

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DR. BRUFSKY

There were two episodes of grade I/II renal insufficiency believed related to zoledronic acid. However, there were no significant differences between the two study arms in arthralgia, myalgia, fever, or other side effects. And among the 602 study participants, there was not a single confirmed case of osteonecrosis of the jaw, a side effect that has been reported with bisphosphonates.

Audience member Dr. Hope S. Rugo of the University of California, San Francisco, asked if, in light of the lack of a major reduction in fractures in the up-front zoledronic acid group, it would be more prudent to stick to the delayed-initiation strategy. That strategy is in accord with current American Society of Clinical Oncology guidelines, which recommend individualized therapy.

Dr. Brufsy replied that, had Z-FAST been a 3,000- or 4,000-patient trial, he suspects—based upon the highly significant differences observed in surrogate end points—that the trend for fewer fractures with up-front therapy would have achieved significance.

"I'm not certain that every woman [on an AI] should get these drugs, but I'm becoming more convinced of that over time," he added.

Dr. Brufsky is a member of an international expert panel that develops alternative evidence-based guidelines for prevention of AI-associated bone loss in breast cancer patients. In a separate presentation at the symposium, fellow panelist Dr. Peyman Hadji outlined the group's recommendations.

Based on a systematic literature review, the panel recommends that, in addition to calcium and vitamin D supplements, any breast cancer patient initiating AI therapy with a baseline T score below –2.0 should be placed on zoledronic acid.

Moreover, up-front zoledronic acid also will be recommended by the expert panel for patients receiving an AI who have any two of the following risk factors: a T score below –1.5, age greater than 65 years, a personal history of a fragility fracture after age 50 years, a family history of hip fracture, or a history of more than 6 months of oral corticosteroid therapy, added Dr. Hadji of Philipps University, Marbug, Germany.

Z-FAST was sponsored by Novartis Oncology.

Dr. Brufsky and Dr. Hadji are on the speakers bureau for Novartis. ■

Metformin May Have Novel Role as Breast Cancer Drug

BY BRUCE JANCIN
Denver Bureau

San Antonio — Metformin, an old and familiar diabetes drug, might have a future in the prevention and adjuvant therapy of breast cancer.

Accumulating evidence from epidemiologic, cell culture, and animal studies suggests that metformin has an antineoplastic effect. The drug is in ongoing randomized clinical trials with biomarker end points in breast cancer patients. If outcomes prove favorable, larger trials with clinical end points in the prevention and adjuvant settings are likely, Dr. Michael Pollak said at the annual San Antonio Breast Cancer Symposium.

Although metformin is often described as an insulin sensitizer because it reduces hyperinsulinemia in insulin-resistant patients, he and his colleagues have shown that it acts as a growth inhibitor in human epithelial cells, including breast cancer cells, by activating the adenosine monophosphate kinase pathway (Cancer Res. 2006;66:10269-73).

This finding, coupled with the fact that metformin reduces circulating insulin and insulinlike growth factor (IGF) levels, provides mechanisms to explain the observation in epidemiologic studies that women on metformin appear to have a reduced likelihood of developing breast cancer, and that breast cancer patients on metformin have a better prognosis, according to Dr. Pollak, professor of oncology and medicine and director of the Cancer Prevention Program at McGill University, Montreal.

He explained that the classic medical school teaching regarding insulin is incomplete. The conventional wisdom holds that insulin is a product of pancreatic β cells that regulates systemic energy balance by acting on insulin-sensitive liver, fat, and muscle tissues. In reality, insulin is present and regulates cell behavior even in simple organisms without a pancreas. Moreover, both normal and transformed human epithelial cells contain copious receptors for insulin and IGF-1.

Body mass index, caloric intake, physical exercise, birth weight, and the timing of the adolescent growth spurt are all breast cancer risk or prognosis factors. And they have a common underlying theme: All are related to insulin and IGF signaling and other hormonal mediators of energy balance and growth regulation.

Patients with high insulin or C-peptide levels may be most likely to benefit from metformin.

DR. POLLAK

Greater BMI means higher circulating insulin and IGF-1 levels, and while higher BMI is only modestly associated with increased breast cancer risk, it is more strongly related to worse mortality in women who have the malignancy. Hence, the increasing prevalence of obesity in North America could begin to erode the substantial improvements in breast cancer mortality seen in the last two decades, the endocrinologist said.

In one recent hypothesis-generating metformin study, Dr. Josie M.M. Evans and coworkers at the University of Dundee (Scotland) evaluated roughly 11,876 patients with newly diagnosed type 2 diabetes, of whom 923 were subsequently diagnosed with cancer. The adjusted relative risk of malignancy in long-term metformin users was reduced by 44%, compared with nonusers (BMJ 2005;330:1304-5).

In another population-based cohort study, investigators at the Institute of Health Economics, Edmonton, Alta., identified 10,309 Saskatchewanians with type 2 diabetes. During an average of 5.4 years of follow-up after their diagnosis, 407 cancer-related deaths occurred. Cancer mortality was 3.5% in metformin users, 5.8% in insulin users, and 4.9% in individuals on sulfonylurea monotherapy. After adjustment in a multivariate Cox regression analysis, cancer-related mortality was 30% greater in sulfonylurea users than in metformin users. In insulin users, it was 90% higher than in metformin users (Diabetes Care 2006; 29:254-8).

Dr. Pollak speculated that the subgroup of breast cancer patients most likely to benefit from metformin in terms of reduced recurrence and mortality risks are those with high circulating insulin or C-peptide levels. This would include not only the many patients with a high BMI, but also what he called normal-weight metabolically obese individuals.

"These people have high insulin levels even though they're thin. There are lots of such individuals in affluent societies," he said.

Even as Dr. Pollak and others focus on metformin as a possible breast cancer agent, more than a dozen pharmaceutical companies are developing drugs targeting the IGF-1 signaling pathway for the treatment of various cancers. The products in the pipeline fall into three strategies: antiligand antibodies, antireceptor antibodies, and small-molecule tyrosine kinase inhibitors. Most are in preclinical or phase I studies.

In contrast, nearly 35 million prescriptions per year are written for the generic version of metformin alone. The drug is well tolerated and its safety profile is thoroughly established. ■

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