Low Vitamin D Tied to Bone Loss in Breast Cancer

BY JANE SALODOF MACNEIL
Southwest Bureau

ATLANTA — Vitamin D supplementation should be considered for postmenopausal breast cancer patients treated with aromatase inhibitors, Dr. Per E. Lønning reported at the annual meeting of the American Society of Clinical Oncology.

"Low vitamin D status could be one of the factors predisposing patients to breast cancer," said Dr. Lønning, a professor at Haukeland University in Bergen, Norway.

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"Low vitamin D status could be one of the factors predisposing patients to breast cancer," said Dr. Per E. Lønning (left).

Postmenopausal breast cancer patients who were treated with exemestane and had vitamin D deficiency lost bone mineral density (BMD) at a higher rate than all other patients in a Norwegian trial, according to Dr. Lønning, who presented the trial's results.

The double-blind study enrolled early breast cancer patients at six sites between January 1999 and October 2001. Participants were postmenopausal with estrogen receptor–negative or progesterone receptor–positive breast cancer. Median patient age was 59.5 years, and all had a low risk of breast cancer recurrence after surgery.

Among the patients enrolled in the randomized, controlled trial, 128 of 147 (87%) had low levels of vitamin D, defined as 30 ng/mL or less. Investigators randomized 73 women to 25 mg of oral exemestane daily and 74 women to a daily placebo for 2 years. Local guidelines did not routinely offer adjuvant endocrine therapy at the time of the study, the investigators noted. Mean vitamin D levels were reported as 21.6 ng/mL for the exemestane arm and 22.6 ng/mL for the control group.

Postmenopausal breast cancer patients who were treated with exemestane and had vitamin D deficiency lost bone mineral density at a higher rate.

Average patient change in femoral neck BMD was –4.7% after 2 years of treatment with exemestane, an aromatase inhibitor. Placebo patients with low vitamin D also had bone loss in the femoral neck, but the reduction was 3.0%.

Women with normal vitamin D levels had similar outcomes whether they were treated with exemestane or placebo: reductions of 3.7% and 3.3%, respectively.

"It has not fully been examined that breast cancer patients on average have a poorer vitamin D status in comparison to the normal population," he added.

An annual BMD loss of 0.5% is normal for postmenopausal women, according to Dr. Lønning and his fellow investigators from the Norwegian Breast Cancer Screening Program. Interviewed during the poster session where he presented trial data, he said low vitamin D levels could be expected in about 50% of postmenopausal women in Norway. However, he warned against assuming that low vitamin D levels are entirely explained by reduced sun exposure in northern latitudes, because people in other climates are spending more time indoors and out of the sun.

While the investigators reported some significant differences in subgroups and "a trend toward higher loss of BMD in the femoral neck" among women with low vitamin D during the 2 years of exemestane treatment, low vitamin D did not appear to affect lumbar spine BMD as much. The reductions were 3.4% for 52 women deficient in vitamin D who completed the study on exemestane and 2.5% for 59 women who stayed on placebo.

"Vitamin D has influence on compact bone, not trabecular bone," Dr. Lønning said. ■

HERA Trial Shows Better Overall Survival With Trastuzumab

BY JANE SALODOF MACNEIL
Southwest Bureau

ATLANTA — New results from the international Herceptin Adjuvant (HERA) trial show that taking trastuzumab for 12 months after standard chemotherapy significantly reduced the risk of death for early-stage HER2-positive breast cancer patients.

At a median follow-up of 2 years, 1,703 patients treated with trastuzumab (Herceptin), a monoclonal antibody, also continued to have better disease-free survival, compared with 1,698 patients in the observation arm of the study.

Risk of cardiotoxicity remained low in the updated data presented by Dr. Ian Edward Smith at the annual meeting of the American Society of Clinical Oncology.

The researchers for the phase III trial, conducted by the Swiss-based Roche pharmaceutical company and the Breast International Group (BIG), previously reported a disease-free survival benefit based on 1-year data (N. Engl. J. Med. 2005;353:1659-72). They have yet to report on a third arm of the study that randomized 1,694 women to 24 months of adjuvant therapy with trastuzumab.

In a discussion of the new data, Dr. Clifford A. Hudis described HERA and other studies of adjuvant trastuzumab as "amazingly consistent." The value of trastuzumab is established, but the best way to incorporate it into therapy for early-stage human epidermal growth factor receptor 2 (HER2)–positive patients still needs to be resolved, said Dr. Hudis, chief of the breast cancer service at Memorial Sloan-Kettering Cancer Center in New York.

"Approval and use in the adjuvant setting is appropriate, and we should be working on that at this time," he said.

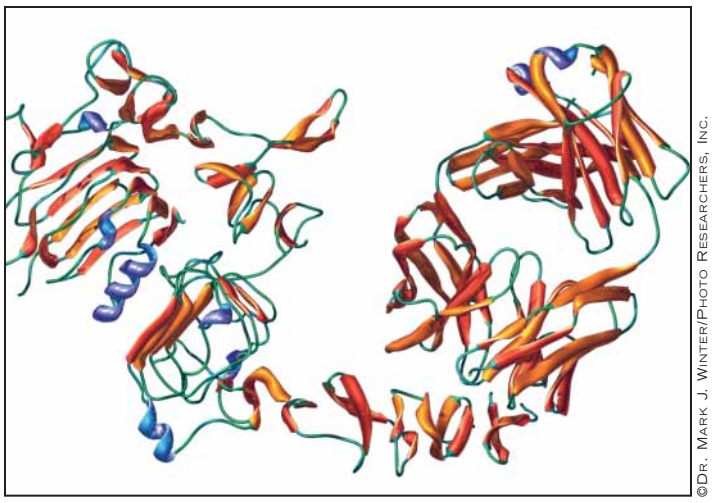
In the 2-year data reported by Dr. Smith, head of the breast unit at Royal Marsden Hospital in London, an intent-to-treat analysis found that 92.4% of the trastuzumab arm and 89.7% of the observation group were alive at 3 years (hazard ratio 0.66). Disease-free survival was 80.6% in the trastuzumab arm and 74.3% in the observation group (hazard ratio 0.64).

Dr. Smith reported similar results in a censored analysis that did not count 861 observation arm patients who switched to trastuzumab after the first-year results were announced last year. He predicted the desire of patients to cross over to the treatment arm of a trial that reports significant benefit in its preliminary analysis will be a recurring issue in breast cancer trials.

Only intent-to-treat analysis was presented for the rest of the data. Time to distant recurrence of disease favored trastuzumab: 85.7% did not have distant disease at 3 years vs. 79.4% of the control group (hazard ratio 0.60).

There were more central nervous system events in patients treated with trastuzumab, however. Dr. Smith speculated that trastuzumab may not penetrate the CNS sufficiently or these events might be masked in the observation arm because some of these women had other distant events before brain metastases.

Subgroup analyses of the trastuzumab arm found "no evidence of substantial difference in relative treatment effect between subgroups and no evidence of any subgroup in which there is less efficacy," Dr. Smith said. He singled out nodal status and neoadjuvant therapy, emphasizing that trastuzumab was equally effective whether the women were lymph node negative or lymph node positive at entry into the trial and whether they had neoadjuvant therapy.



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Trastuzumab, portrayed in this molecular model, binds to HER2 receptors and slows the spread of breast cancer.

Conducted at 480 sites in 39 countries, the trial allowed wide latitude in the types of prior regimens the women received. Dr. Smith noted that only 26% had prior taxane therapy. About 11% had neoadjuvant therapy.

About half of the women were estrogen-receptor negative, he said, proposing that it may be the largest trial ever conducted in ER-negative women. While the arms were well balanced, he characterized the overall population as young, with a median age of 49 years. Only 16% were over the age of 60.

Not unexpectedly, serious adverse events were more frequent with trastuzumab: 9.2% of patients had at least one, compared with 6.6% of the control group. All told, 172 women (10.1%) on trastuzumab withdrew from treatment.

Although deaths resulting from adverse events were more common in patients on trastuzumab, Dr. Smith said none were related to the drug. The only cardiac death occurred in a patient randomized to observation.

Other measures showed that cardiac toxicity occurred in small proportions of women on trastuzumab: severe congestive heart failure in 0.6%, symptomatic congestive heart failure in 2.1%, and a confirmed significant drop in left ventricular ejection fraction in 3.0%.

"The risk of cardiac toxicity remains low," Dr. Smith said.

He promised continued safety evaluation in the ongoing long-term follow-up of these patients. Of particular interest, he said, will be data on patients who took trastuzumab for 24 months. The greatest risk of recurrence has been during the first year of the study, and investigators are hoping that longer therapy will be more protective.

Trial sponsor Roche markets trastuzumab internationally and has a majority interest in Genentech Inc., which markets the drug in the United States. ■