Zoledronic Acid Sustains Bone in Breast Ca Patients

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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 the annual 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 analog, 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 a separate study presented at the conference, it was reported that zoledronic acid also effectively prevents cancer therapy-induced bone loss in postmenopausal women with early-stage breast cancer on adjuvant aromatase inhibitor therapy.

In clinical practice, the aromatase inhibitors increasingly are replacing tamoxifen, long the standard adjuvant hormonal therapy, because they provide a markedly greater reduction in recurrence along with less risk of endometrial cancer and thromboembolic events.

The price for these advantages has been the greater risk of osteoporosis and fractures associated with aromatase inhibitor therapy.

But prophylactic zoledronic acid appears to erase that downside.

While it is widely appreciated that postmenopausal breast cancer patients face increased risk of accelerated bone loss, the osseus 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 4-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 experienced no significant change in BMD, the surgeon said.

Separately, Adam Brufsky, M.D., presented preliminary 6-month results from Z-FAST, a 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 upfront 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 upfront and decreased in those assigned to delayed bisphosphonate therapy. Biochemical markers of bone turnover decreased from baseline to 6 months in the upfront zoledronic acid group, while increasing or remaining unchanged in the delayed treatment arm.

Patients on either combination who received zoledronic acid had no significant change in BMD.

DR. GNANT

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.

Until zoledronic acid receives 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 for 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. ■

Switch Out Tamoxifen to Improve Ca Outcomes

SAN ANTONIO — Switching postmenopausal breast cancer patients to an aromatase inhibitor following 2-3 years of adjuvant tamoxifen results in markedly better disease-free survival than the traditional 5 full years of tamoxifen, according to three major randomized trials presented at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Raimund Jakesz, M.D., recommended that breast cancer patients who fit the profile of participants in two European clinical trials he reported on at the conference be routinely switched to 3 years of anastrozole (Arimidex) after 2 years of tamoxifen.

He reported on more than 3,100 breast cancer patients in the AstraZeneca-sponsored Austrian Breast and Colorectal Cancer Study Group Trial 8 and the German Adjuvant Breast Cancer Group ARNO 95 study who were randomized to the standard 5 years of adjuvant tamoxifen or to 2 years of tamoxifen followed by 3 years of anastrozole.

The 3-year rate of freedom from locoregional recurrence, distant metastasis, and contralateral breast cancer was 95.8% with tamoxifen/anastrozole vs. 92.7% with tamoxifen. The likelihood of survival free of distant recurrence was 39% greater with tamoxifen followed by anastrozole, said Dr. Jakesz, professor of surgery at the University of Vienna.

All participants in the two randomized trials were postmenopausal, had hormone receptor–positive disease, and underwent breast-conserving therapy. One-fourth were node positive. None received chemotherapy. Forty percent were under 60 years old. Most had small, well-differentiated tumors.

In a separate presentation, Charles Coombes, M.D., gave an update on the Intergroup Exemestane Study (IES), in which 4,740 postmenopausal breast cancer patients were randomized to 5 years of adjuvant tamoxifen or switched to exemestane (Aromasin) after 2-3 years. At a median 37 months' follow-up, local or distant recurrence had developed in 264 women treated with tamoxifen and 193 switched to the aromatase inhibitor. That translated into a 27% increase in disease-free survival in patients who switched. Twelve cases of contralateral breast cancer occurred in the tamoxifen/exemestane group vs. 26 in those on tamoxifen alone.

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DR. JAKESZ

A particularly intriguing finding is that there have been significantly fewer new primary cancers at sites other than the breast with exemestane: 46 vs. 59 in the tamoxifen-only arm. There have been 6 cases of lung cancer with tamoxifen/exemestane vs. 13 with tamoxifen, and 2 cases of melanoma vs. 5 cases with tamoxifen only. However, 20 acute MIs have occurred in patients switched to the aromatase inhibitor vs. 8 MIs in the tamoxifen-only group, said Dr. Coombes, director of the Cancer Research UK Laboratories at Imperial College, London.

Based upon the highly favorable IES data, Pfizer announced it has submitted a supplemental New Drug Application seeking Food and Drug Administration approval for exemestane as adjuvant therapy in postmenopausal women with hormone receptor–positive early-stage breast cancer. At present, tamoxifen and anastrozole are the sole drugs with that indication.

A midcourse switch from tamoxifen to an aromatase inhibitor makes a lot of sense, Hope S. Rugo, M.D., said at a satellite symposium held in conjunction with the San Antonio conference. Tamoxifen is of proven benefit in preventing recurrent breast cancer. It's a good drug with favorable ancillary effects on bone mineral density and the cardiovascular risk profile. But resistance can occur as early as 12-18 months after starting.

Plus, the most serious side effects associated with tamoxifen—endometrial cancer and thromboembolism—become more likely with longer treatment. Stopping tamoxifen early might prevent some of these major adverse events while still providing protection against the increased fracture risk associated with 5 years of anastrozole in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, said Dr. Rugo, director of the breast oncology clinical trials program at the University of California, San Francisco, Comprehensive Cancer Center.

To date the switch trials have shown a higher incidence of osteoporosis but not a significant rise in fractures, compared with 5 years of tamoxifen alone, she noted. ■

More Educated Breast Ca Patients Use More CAM

SAN ANTONIO — The more years of formal education a breast cancer patient has, the more likely she is to use complementary and alternative medicine in conjunction with adjuvant chemotherapy, Eleanor Glass reported at the annual breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Her survey of 700 breast cancer patients who received chemotherapy and/or adjuvant hormone therapy showed that the majority—55%—used complementary and alternative medicine (CAM) before, during, or afterward. A total of 27% of patients reported using CAM during all three time periods.

CAM usage was strongly related to education level. Overall, 30% of patients without a high school degree reported using CAM, as did 50% with a high school degree, more than two-thirds of women with a college degree, and 70% with graduate education, said Ms. Glass of the University of Cincinnati.

The most commonly used CAM therapies, in descending order of frequency, were vitamin E, vitamin C, vitamin B_6, green tea, selenium, echinacea, garlic extract, soy supplements, and ginkgo biloba. ■