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Bisphosphonates and Beyond: Managing Bone Density and Reducing Breast Cancer

SAN ANTONIO – Bisphosphonates are routinely given to women with postmenopausal breast cancer, but new data suggests that these agents may play a role in reducing recurrent breast cancer as well.

Theresa Guise, M.D., professor of medicine and Jerry W. and Peg S. Throgmartin professor of oncology in the Division of Endocrinology at the Indiana University School of Medicine, will moderate a press conference on this new data at the CTRC-AACR San Antonio Breast Cancer Symposium.

The press conference will take place on Thursday, Dec. 10, 2009, at 12:30 p.m. CT, in room 217C of the Henry B. Gonzales Convention Center. Reporters who cannot attend in person can participate by using the following information:

- U.S. & Canada: (888) 282-7404
- International: (706) 679-5207
- Access Code: 39115588
- Topic: AACR

The following abstracts will be presented at this press conference:

4083. The Effect of Zoledronic Acid on Aromatase Inhibitor-Associated Bone Loss in Postmenopausal Women with Early Breast Cancer Receiving Adjuvant Letrozole: The Z-FAST Study 5-Year Final Follow-Up

Zoledronic acid is both safe and effective in preventing bone loss in postmenopausal women with breast cancer who are treated with aromatase inhibitors, according to data presented at the CTRC-AACR San Antonio Breast Cancer Symposium.

“Women who take aromatase inhibitors need some sort of bone protection, and this five-year data show that zoledronic acid is a viable option,” said Adam Brufsky, M.D., Ph.D., associate professor of medicine, associate chief of hematology-oncology, and associate director for clinical investigation, University of Pittsburgh Cancer Institute.

Brufsky estimates that between 20,000 to 30,000 women a year will benefit from this therapy and that number is growing. Anastrozole, currently sold as Arimidex by AstraZeneca, is scheduled to go off patent within the next few years.

“Women who are on Medicare tend to go with tamoxifen because the cost of anastrozole puts them squarely in the donut hole of Medicare Part D, but once the cost barrier is removed there will likely be a mass switch to the aromatase inhibitor, which will necessitate the need for bone protection,” said Brufsky.

Beyond the aging population, use of zoledronic acid could increase even further if the signs that it prevents breast cancer recurrence continue in larger studies.

Brufsky’s study, Z-FAST (Zometa-Femara Adjuvant Synergy Trial), focused on 602 postmenopausal women with stage I to IIIa estrogen or progesterone receptor-positive breast cancer. The researchers randomized patients to immediate zoledronic acid or delayed zoledronic acid. The delayed group received it only if the T-score dropped below two or a clinical fracture occurred.

After five years, patients in the immediate treatment arm had a bone mineral density increase of 6.2 percent in their lumbar spine area, while those in the delayed arm had a decrease of 2.4 percent. In the hip area, the increase was 2.6 percent with immediate treatment compared with a 4.1 percent decrease with delayed treatment.

Fractures occurred in 10.7 percent of the patients treated immediately and 12.4 percent of the patients who received delayed treatment.

There were no serious renal events and no osteonecrosis of the jaw, which confirmed that the drug was safe and well tolerated.

21. Oral Bisphosphonate and Breast Cancer: Prospective Results from the Women's Health Initiative (WHI)

Results of a new analysis of data from the Women’s Health Initiative (WHI) observational study showed that women who used bisphosphonates, which are commonly prescribed bone-strengthening pills, had significantly fewer invasive breast cancers than women who did not use bisphosphonates. These findings were presented at the CRTC-AACR San Antonio Breast Cancer Symposium.

In the 150,000-plus cohort of generally healthy postmenopausal women, the researchers found that women who used bisphosphonates, mostly alendronate, which is sold as

Fosamax by Merck, had 32 percent fewer cases of invasive breast cancer compared to women who did not use such drugs.

“The idea that bisphosphonates could reduce breast cancer incidence is very exciting because there are about 30 million prescriptions for these agents written annually in the United States targeting bone health, and more could easily be used to counteract both osteoporosis and breast cancer,” said the study’s lead investigator, Rowan Chlebowski, M.D., Ph.D., medical oncologist at the Los Angeles Biomedical Research Institute at Harbor-University of California, Los Angeles Medical Center.

The concept arose from findings in a report on an adjuvant breast cancer trial where use of the bisphosphonate zoledronic acid given intravenously every six months resulted in fewer contralateral breast cancers.

“It appeared to make bone less hospitable to breast cancer,” Chlebowski said.

However, since bisphosphonates are prescribed for women with low bone mineral density and low bone mineral density has been associated with lower breast cancer incidence, a means to control for potential differences between women prescribed bisphosphonate and those not prescribed bisphosphonate in the cohort was needed.

Given that, Chlebowski and colleagues devised a way to control for use of bisphosphonates in the WHI. About 10,000 of the participants had bone mineral density analysis as part of the study, and for the rest they used a 10-item hip fracture predictive score to measure bone density. The researchers were able to correlate the findings from the women who had bone mineral density tests to findings from the predictive score in order to correct for any potential difference in bone density in women using bisphosphonates compared to non-users. Studying 2,216 WHI participants who were using bisphosphonates when they entered the study, the researchers found that only 64 women developed breast cancer, and most of those cases (50) were estrogen receptor positive. Overall, there was a mean 32 percent fewer breast cancers in women using bisphosphonates compared to women who did not. There were 30 percent fewer estrogen receptor-positive cancers and 34 percent fewer estrogen receptor-negative cancers in bisphosphonate users. The latter finding was not statistically significant as there were very few receptor-negative cases.

“Bisphosphonates reduce angiogenesis and stimulate immune cells responsible for tumor cell surveillance as potential mediators,” Chlebowski said. “This association needs to be studied further. While we currently have several options for reducing receptor-positive breast cancers, none are available for receptor-negative cancers.”

Several ongoing adjuvant breast cancer trials evaluating oral and intravenous bisphosphonate will be available in the near future to provide randomized clinical trial evidence regarding their influence on new contralateral breast cancer risk, Chlebowski said

27. Use of Bisphosphonates and Risk of Postmenopausal Breast Cancer

The use of bisphosphonates for more than one year was associated with a 29 percent reduction in the risk of postmenopausal breast cancer, according to results presented at the CTRC-AACR San Antonio Breast Cancer Symposium.

Lead researcher Gad Rennert, M.D., Ph.D., chairman of the Department of Community Medicine and Epidemiology at the Carmel Medical Center of Clalit Health Services and a faculty member at the Technion-Israel Institute of Technology in Israel, said these data help shed light on a possible new pathway for breast cancer prevention.

“We have identified a new class of drugs that is associated with a reduced risk of breast cancer, and if proven in randomized trials, we may be able to recommend it to postmenopausal women for this purpose,” said Rennert.

Rennert and colleagues extracted data from the Breast Cancer in Northern Israel Study, which is a population-based, case-control study. They evaluated the use of bisphosphonates for at least five years in 4,575 postmenopausal study participants using a structured interview.

The self-reported, long-term use of bisphosphonates prior to diagnosis was associated with a significant reduced relative risk for breast cancer by approximately 34 percent.

This reduction remained significant, at 29 percent, even after adjusting for a large variety of risk factors for breast cancer such as age, fruit and vegetable consumption, sports activity, family history of breast cancer, ethnic group, body mass index, calcium supplement and hormone replacement therapy use, number of pregnancies, months of breastfeeding and age at first pregnancy.

Moreover, the breast tumors identified among patients who used bisphosphonates were more often estrogen receptor positive and less often poorly differentiated.

“These tumors are the type that are associated with a better prognosis,” said Rennert.

22. AA Comparison of Denosumab Versus Zoledronic Acid on the Incidence of Skeletal-Related Events in Breast Cancer Patients with Bone Metastases

Among patients with bone metastasis from breast cancer, denosumab was superior to zoledronic acid in reducing the incidence of complications from bone metastases.

“Denosumab prevented more events, was better tolerated and is more convenient for patients,” said Alison Stopeck, M.D., associate professor of medicine at the University of Arizona Cancer Center.

Stopeck and colleagues enrolled 2,048 patients with bone metastasis who had never received treatment with intravenous bisphosphonates. They randomly assigned patients to

treatment with subcutaneous denosumab or intravenous zoledronic acid every four weeks.

Denosumab works by inhibiting *RANKL*, which regulates osteoclast activity and function and has been linked with increased bone loss and complications from bone metastases.

Full data will be presented at the CTRC-AACR San Antonio Breast Cancer Symposium.

2009. Randomised Placebo Controlled Trial Studying Short Term Biological Effects of the Combination of Letrozole and Zoledronic Acid on Invasive Breast Cancer

Preoperative combination therapy with letrozole and zoledronic acid is safe and effective, but more research is needed to verify the impact on overall survival or reduced morbidity.

Nigel J. Bundred, M.D., professor in surgical oncology at the University Hospital of South Manchester and the University of Manchester, United Kingdom, and colleagues conducted this study to determine whether the addition of the bisphosphonate zoledronic acid to treatment with letrozole increased cell death or lowered proliferation.

Letrozole is an oral, non-steroidal aromatase inhibitor used for treatment of local or metastatic breast cancer that is hormone receptor-positive. Zoledronic acid, also known as zoledronate, is used to prevent bone fractures in patients with cancers like prostate cancer and multiple myeloma, or for treatment of bone metastases.

Researchers conducted the study in 109 postmenopausal women with early, invasive hormone receptor-positive breast cancer. Patients were randomized and treated for 14 days with placebo, letrozole 2.5 mg per day, or to letrozole with adjuvant use of zoledronic acid 4 mg intravenously two to four days before surgery.

While the addition of zoledronic acid was safe, results showed no other benefits compared with letrozole use alone.

“Letrozole significantly lowered proliferation,” said Bundred. “A combination of letrozole and a bisphosphonate, while lowering proliferation, did not do significantly greater than letrozole on its own.”

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The mission of the CTRC-AACR San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for breast cancer patients. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR) and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor, and the AACR’s scientific prestige in basic, translational and clinical cancer research to expedite the delivery of

the latest scientific advances to the clinic. The 32nd annual symposium is expected to draw more than 8,500 participants from more than 90 countries.

Presenter Name: Adam Brufsky, M.D., Ph.D.

Institution: Univ. of Pittsburgh Cancer Institute

Abstract Number: 4083

Abstract Title: The Effect of Zoledronic Acid on Aromatase Inhibitor-Associated Bone Loss in Postmenopausal Women with Early Breast Cancer Receiving Adjuvant Letrozole: The Z-FAST Study 5-Year Final Follow-Up

Abstract Body:

Background: Aromatase inhibitor (AI) therapy effectively increases disease-free survival in postmenopausal women (PMW) with ER+ and/or PR+ breast cancer (BCa). However, the use of AIs results in nearly complete ablation of estrogen production which can lead to accelerated bone loss and increased fracture risk. The Z-FAST study evaluated the efficacy and safety of zoledronic acid (ZOL) in preventing AI associated bone loss in PMW with early breast cancer (EBC) who received adjuvant letrozole (LET).

Material and Methods: 602 PMW with stage I-IIIa ER+ and/or PR+ BCa starting LET (2.5 mg qd x 5 yrs) were randomized (1:1) to upfront ZOL (4 mg IV q 6 mos) vs delayed ZOL. The delayed arm (D) received ZOL when either the post-baseline T-score decreased to <-2 or a clinical fracture occurred. All patients (pts) were treated with calcium and vitamin D. The primary endpoint, the percent change in lumbar spine (LS) bone mineral density (BMD) at 12 mos, was previously reported (JCO; 25:829, 2007). The 5 year (5y) final study results are reported here.

Discussion: Baseline characteristics were similar between groups. 180 pts in upfront ZOL arm (U) and 175 pts in D completed full 5y study. Of pts with BMD data available, U (n=140) showed a mean increase of 6.2% in LS BMD while D (n=132) showed a mean decrease of 2.4%, resulting in an absolute difference of 8.6% (p<0.001). U (n=141) showed a mean increase of 2.6% in total hip (TH) BMD while D (n=132) showed a mean decrease of 4.1%, resulting in an absolute difference of 6.7% (p<0.001). When BMD data in D was excluded after pts started ZOL (censored analysis), the absolute difference in LS and TH BMD between the two arms was 11.3% and 8.7%, respectively. Among pts with baseline LS T-score between -1 and -2, 27.9% (19) U pts [8.6% (7) D pts] returned to normal T-score (T-score >-1), and no U pts as compared to 4.9%(4) D pts became severely osteopenic (T <-2). 17.7% (53) D pts met criteria that required initiation of ZOL. Although the study was not designed to detect a significant difference in the fracture rate between treatment arms, fractures occurred in 10.7% (29) U pts and 12.4% (33) D pts. Administration of ZOL q 6 mos for up to 5y was safe and well tolerated. No serious renal adverse events suspected related to ZOL and no confirmed osteonecrosis of the jaw cases (ONJ) were reported. Disease recurrence including death due to disease progression was reported in 7.0%, 95% C.I. (3.7%-10.3%) from K-M (16) pts in U, and 8.8%, 95% C.I. (5.2%-12.5%) (21) pts in D.

Conclusion: The 5y follow-up of the Z-FAST trial show that the overall difference in the percentage change in BMD between U and D, at both LS and TH, progressively increased from baseline through 5y. These data demonstrate that ZOL 4mg IV q 6 mos is effective in preventing bone loss associated with adjuvant AI therapy in PMW with EBC.

First Name: Rowan Chlebowski, M.D., Ph.D.

Institution: Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center

Abstract Number: 21

Abstract Title: Oral Bisphosphonate and Breast Cancer: Prospective Results from the Women's Health Initiative (WHI)

Abstract Body:

Background: Emerging clinical evidence suggest intravenous bisphosphonates may directly inhibit breast cancer (Gnant SABCS 2008) while oral bisphosphonates in US clinical practice have received limited evaluation regarding breast cancer influence.

Methods: To investigate associations between oral bisphosphonates and invasive breast cancer we examined data for 151,592 postmenopausal women enrolled in the WHI. Information was collected on breast cancer risk factors and oral bisphosphonate use. To control for bone mineral density (BMD) we employed a published hip fracture prediction model which did not incorporate BMD (Robbins 2007) against the 10,296 WHI participants who had baseline total hip BMD determination. Breast cancers were centrally adjudicated by pathology report review. Cox proportional hazards regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: Of the 151,592 participants, 2,216 were oral bisphosphonate users at entry (90% alendronate, 10% etidronate). An analysis comparing hip fracture risk score to BMD in those with both found a significant correlation (regression line = $.79-.0478 \log$ predicted hip fracture, $r=0.43$). As a result, the hip fracture risk score was used to control for potential BMD group differences. HRs for invasive breast cancer by bisphosphonate use are outlined below after 7.8 (1.7) mean years (SD).

* Rate/1000 women years of follow-up

**Cox proportional hazards analyses adjusted for age, ethnicity, smoking, alcohol use, physical activity, BMI, mammograms, prior hormone use, calcium, vitamin D, hip fracture risk score, Gail risk score and stratified on WHI trial randomization arm.

Conclusion: There was a statistically significant association between oral bisphosphonate use and lower invasive breast cancer incidence with fewer ER positive breast cancers and a non-significant trend for ER negative breast cancers in bisphosphonate users. This result suggests oral bisphosphonates may have direct inhibiting effects on breast cancer.

OBJECTS

Bisphosphonate Use		Breast Cancer Incidence **
No	Yes	

Invasive Breast Cancer	N	Rate*	N	Rate	HR	95% CI	P-value
Total	5092	4.38	64	3.29	0.68	(0.52-0.89)	< .01
ER positive	3829	3.28	50	2.56	0.70	(0.52-0.95)	0.02
ER negative	717	0.61	8	0.41	0.66	(0.31-1.39)	0.27

Presenter Name: Gad Rennert, M.D., Ph.D.

Abstract Number: 27

Abstract Title: Use of Bisphosphonates and Risk of Postmenopausal Breast Cancer

Institution: Carmel Medical Center of Clalit Health Services

Abstract Body:

Background Bisphosphonates are commonly used for the treatment of osteoporosis and for prevention and treatment of skeletal lesions due to malignancy. However the association between the use of bisphosphonates and the risk of developing breast cancer has not been reported.

Methods The Breast Cancer in Northern Israel Study (BCINIS) is a population-based case-control study in northern Israel of breast cancer cases and age/clinic/ethnic-group matched controls. Use of bisphosphonates for at least 5 years was assessed in 4,575 postmenopausal cases and controls using a structured interview. It was further validated by data from prescription records among participants for whom they were available.

Results The self-reported long-term use of bisphosphonates prior to diagnosis was associated with a significantly reduced relative risk of breast cancer (Odds Ratio=0.66, 95% CI: 0.47-0.93). This association remained significant in a pharmacy records based analysis after adjustment for age, fruit and vegetable consumption, sports activity, family history of breast cancer, ethnic group, BMI, use of calcium supplements, HRT use, number of pregnancies, months of breast feeding and age at first pregnancy (OR=0.71, 0.57-0.90). A significant dose response association between length of use of bisphosphonates and breast cancer risk was found. Breast tumors identified in bisphosphonates users were more often ER positive and less often poorly differentiated.

Conclusions The use of bisphosphonates for more than 1 year was associated with a 29% relative reduction in the risk of postmenopausal breast cancer. Tumors developing under bisphosphonates treatment tended to have a favorable prognostic factors profile.

Presenter Name: Alison Stopeck, M.D.

Institution: University of Arizona, Arizona Cancer Center

Abstract Number: 22

Abstract Title: A Comparison of Denosumab Versus Zoledronic Acid on the Incidence of Skeletal-Related Events in Breast Cancer Patients with Bone Metastases

Abstract Body:

Background: Increased osteoclastogenesis and bone destruction leading to skeletal-related events (SREs) is a hallmark of bone metastases from breast cancer. Osteoclast activity is regulated by RANKL, which can be inhibited by denosumab, a fully human monoclonal antibody against RANKL. Denosumab has been shown to increase bone mineral density and reduce fractures in postmenopausal women with low bone mass. Primary efficacy and safety results from a recently completed randomized phase 3 study comparing the effects of denosumab and zoledronic acid (ZA) on the incidence of SREs in patients with breast cancer metastatic to bone are presented separately. Here, we compare the proportion of patients with an SRE between the treatment arms at multiple timepoints.

Methods: Bisphosphonate-naïve patients with bone metastases were randomized 1:1 to receive either subcutaneous (SC) denosumab 120 mg and intravenous placebo, or SC placebo and intravenous ZA 4 mg every 4 weeks (Q4W). All patients were instructed to receive supplemental calcium (≥ 500 mg) and vitamin D (≥ 400 IU). The primary endpoint was time to first on-study SRE (predefined as a pathologic fracture, radiation or surgery to bone, or spinal cord compression).

Results and Conclusion: A total of 2048 patients were enrolled. We anticipate that analyses from this study will be completed by the time of presentation. We plan to present the proportion of patients with an SRE and the 95% confidence interval for each treatment group at multiple timepoints. Data from this important head-to-head study will reveal how denosumab compares with ZA in delaying the time to occurrence of on-study SREs in patients with breast cancer metastatic to bone.

Presenter Name: Nigel J. Bundred, M.D.

Institution: University of Manchester

Abstract Number: 2009

Abstract Title: Randomised Placebo Controlled Trial Studying Short Term Biological Effects of the Combination of Letrozole and Zoledronic Acid on Invasive Breast Cancer

Abstract Body: To determine whether the addition of Zoledronic Acid to endocrine therapy increases apoptosis or decreases proliferation in early invasive breast cancer, a placebo controlled randomised trial comparing 14 days treatment with Letrozole or Letrozole and Zoledronic Acid pre-operatively was performed.

Patients

In total 109 postmenopausal women with early invasive hormone receptor positive breast cancer were randomised (1:1:1) to either placebo, Letrozole 2.5mg/day or Letrozole with Zoledronic Acid 4mg single dose intravenously 2-4 days before definitive surgical excision. Epithelial proliferation and apoptosis were measured on paired baseline and surgical biopsy specimens (after 14 days of treatment) using Ki67 and Activated Caspase 3 immunohistochemistry. Alterations in angiogenic markers (VCAM/VEGF and CD31) were also studied. The primary endpoint was fall in Ki67 between diagnosis and surgical excision.

Results

Overall 109 women were enrolled but paired biopsies were only available for 101 patients.

	Placebo	Letrozole	Let + Zol
n	32	34	35
Absolute Ki67 change (median,range)	-0.8 (-12,12)	8.6 (-14,37)	12.9 (-12,29)
Caspase 3 change (median,range)	0.1 (-3.8, 9.3)	0.4 (-2.7, -4.1)	0.2 (-10.9, -14.4)
Absolute change (Cell turnover index)	-0.3 (-142, -59)	18.9 (-201, 192)	17.7 (-14, 379)

Statistically significant reductions in Ki67 and Cell Turnover Index were seen with Letrozole and Let & Zol ($p \leq 0.001$) but there was no significant difference between Letrozole and Letrozole plus Zoledronic Acid groups ($p = 0.26$). Apoptosis did not change between the three groups.

Conclusion

Letrozole reduces proliferation by 70% when used for 14 days prior to surgery. Zoledronic Acid administration prior to surgery is safe but when administered as a single dose at a median of 3 days before surgery did not significantly increase apoptosis or decrease proliferation compared to Letrozole alone.