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Clodronate Appeared Safe, Modestly Affected Breast Cancer Disease Events

- Low rates of toxicity and adverse events were seen with clodronate.
- Clodronate modestly affected breast cancer disease events.
- Clodronate was more favorable in patients aged 50 years or older at diagnosis.

SAN ANTONIO — A recently presented study revealed that the bisphosphonate clodronate had a low incidence of adverse events and toxicity among patients with breast cancer and may modestly reduce the incidence of distant metastases in postmenopausal women.

The results of B-34, a prospective, randomized, double-blind, phase 3 clinical trial, presented at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium, held Dec. 6-10, 2011, are similar to those of trials on other bisphosphonates in this group of patients, according to Alexander H.G. Paterson, M.D., professor in the departments of medicine and oncology at the University of Calgary in Canada.

He and his colleagues enrolled 3,323 patients with stage I, II or III breast cancer between Jan. 22, 2001, and March 31, 2004. Paterson presented data on the 3,311 patients (99.6 percent) with follow-up information. Slightly more than 75 percent of the patients had pathologically negative axillary nodes, 64 percent were 50 years or older at entry and 22 percent had estrogen receptor (ER)-negative or progesterone receptor (PgR)-negative breast cancer.

Researchers randomly assigned patients to receive three years of clodronate or an oral placebo three times a day. In addition, the patients also underwent surgery (lumpectomies or mastectomies) and received radiation therapy and chemotherapy or hormonal therapy. Median follow-up for patients who were still alive was 7.6 years.

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Five hundred ninety-eight patients experienced disease events, defined as any cancer (either recurrent breast cancer or a new primary) or death (cancer related or otherwise): 286 in the clodronate group and 312 in the placebo group. The relative reduction of events in the clodronate group was about 9 percent compared with the placebo group.

“This reduction was smaller than had been hoped for and was not statistically significant,” Paterson said.

Researchers observed a 16 percent relative reduction in mortality in the clodronate group. They also observed relative reductions of 23 percent and 26 percent in the clodronate group for the occurrence of skeletal and nonskeletal metastases, respectively.

“Although clodronate appeared more favorable for all endpoints, only the comparisons of the distant metastasis-free interval and nonskeletal metastasis-free interval were statistically significant and favorable for the clodronate patients,” Paterson said.

Results also demonstrated that clodronate might perform better for patients aged 50 years or older when diagnosed with breast cancer and for women with ER/PgR-positive nodes. Clodronate was generally tolerable, and the toxicities observed were mainly due to concomitant systemic chemotherapy, according to the researchers. This was the largest study to assess clodronate in a placebo-controlled trial, Paterson said.

“At this point, clinical indications are not absolute, but a tolerable agent that has a known beneficial effect on osteopenia with a small reduction in distant disease recurrence may be of interest to some patients and clinicians,” he said. “The current trials of targeted RANK-ligand inhibitors against placebo are of great interest.”

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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 patients with breast cancer. 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 34th annual symposium is expected to draw nearly 8,000 participants from more than 90 countries.

Presenter: Alexander H.G. Paterson, M.D.

Abstract Number: S2-3

Title: NSABP Protocol B-34: A Clinical Trial Comparing Adjuvant Clodronate vs. Placebo in Early Stage Breast Cancer Patients Receiving Systemic Chemotherapy and/or Tamoxifen or No Therapy – Final Analysis.

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Body: Bisphosphonates reduce the incidence of skeletal-related events (fractures, pain, hypercalcemia) in patients (pts) with bone metastases from breast cancer. By inhibiting osteoclast function and subsequent bone turnover they may inhibit the growth of bone (and other) metastases. Their role in preventing or delaying the development of bone (or other) metastases in pts with early breast cancer is uncertain. Three previous trials of oral clodronate have given mixed results. The largest trial (placebo-controlled) and a smaller open-label trial suggested that oral clodronate benefitted pts with improved bone metastases-free survival (BMFS) and overall survival (OS), but a third open-label study showed no benefit with an apparent detrimental effect on survival. Studies of IV zoledronate in open-label trials in early breast cancer have also shown mixed results: the AZURE trial in pts with node positive breast cancer showed no benefit in disease-free survival (DFS) or OS with a possible effect in pts aged over 60. The ABCSG-12 trial in GnRH (plus tamoxifen or anastrozole) treated women with early breast cancer showed a small DFS benefit for those receiving IV zoledronate but no BMFS or OS benefit.

Methods: B-34 is a prospective, randomized, double-blind, phase III clinical trial in pts with stage 1, 2 or 3 breast cancer assessing oral clodronate 1600mg daily for 3 years compared to placebo given alone or in addition to adjuvant chemo- or hormone therapy. Stratification is by age (<50, +50), number of positive nodes (0, 1-3, 4+) and ER/PR status. The primary end-point is DFS. Secondary endpoints are the incidence of skeletal metastases, OS, relapse-free survival, incidence of non-skeletal metastases, and incidence of skeletal morbid events.

Results: 3323 patients were accrued – 1662 in Group A and 1661 in Group B. As of March 31, 2011, 54 pts were declared ineligible: 23 in Group A and 31 in Group B. The average time on study is 101.3 months. Patient characteristics were evenly distributed throughout both groups.

Approximately 75% of pts in each group had negative axillary lymph nodes and some 78% in each group were ER and/or PR positive. About 64% of pts were age 50 or over. Oral clodronate was generally tolerable, toxicities observed being mainly due to the concomitant systemic chemotherapy. One pt in Group A had a 1 mm area of osteonecrosis on the palatal taurus. Compliance, as expected with trials of oral medications, has been a problem. 1910 pts completed 3 years of therapy. Event rates were slower than anticipated. This final analysis assesses a total of 598 events in the two arms.

Conclusions: This trial is the largest placebo-controlled study of an oral bisphosphonate in patients with early breast cancer and will provide further information on the role of bisphosphonates in breast cancer management.

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