Adjuvant Bisphosphonates

25TH ANNUAL SAN ANTONIO BREAST CANCER SYMPOSIUM 21

A number of biologic effects in bone suggest that bisphosphonates have the potential to retard or prevent the clinical onset of metastatic disease. Three randomized adjuvant trials have yielded conflicting results on this question, although the use of these agents is now considered standard in patients with known lytic bone metastases. A new generation of adjuvant trials is currently evaluating whether bisphosphonates will reduce the rate of bone and nonbone metastases and prolong survival. Another promising research strategy being actively discussed is the combination of a bisphosphonate and an aromatase inhibitor, a logical response to the increased fracture rate observed in the anastrozole arm of the ATAC trial.

PHASE III RANDOMIZED STUDY OF ADJUVANT CLODRONATE WITH OR WITHOUT SYSTEMIC CHEMOTHERAPY AND/OR TAMOXIFEN IN WOMEN WITH EARLY-STAGE BREAST CANCER

Open Protocol

Protocol IDs: NSABP-B-34, CTSU
Projected Accrual: 2,400 patients

Eligibility	Stage I or II breast cancer
ARM 1	Clodronate po qd x 3 years
ARM 2	Placebo po qd x 3 years

Patients may receive adjuvant systemic therapy including tamoxifen at the investigator's discretion.

Study Contact:
Alexander HG Paterson, Chair. Tel: 403-670-1707
National Surgical Adjuvant Breast and Bowel Project

Source: NCI Physician Data Query, October 2002

PHASE III RANDOMIZED STUDY OF ZOLEDRONATE, CALCIUM AND CHOLECALCIFEROL (VITAMIN D) TO PREVENT BONE LOSS IN WOMEN WITH BREAST CANCER RECEIVING ADJUVANT CHEMOTHERAPY — Open Protocol

Protocol ID: CLB-79809
Projected Accrual: Approximately 400 patients

Eligibility	Stage I-III or Stage IV due solely to supraclavicular node involvement
ARM 1	Zoledronate q3 months, months 1-24, + (calcium + vitamin D) qd, months 1-36
ARM 2	(calcium + vitamin D) qd, months 1-36 + zoledronate q3 months, months 13-36

Patients receive adjuvant chemotherapy ± tamoxifen

Study Contact:
Charles L Shapiro, Chair. Tel: 614-293-7530
Cancer and Leukemia Group B

Source: NCI Physician Data Query, October 2002

PHASE III TRIALS OF ADJUVANT CLODRONATE (1600mg PO qd) FOR EARLY STAGE BREAST CANCER

Author	Number of pts/site	Clinical characteristics	Duration of therapy (yrs)	Placebo-controlled	Reduction in skeletal mets	Reduction in nonskeletal mets	Survival advantage
Diel et al.	302/single institution	Bone narrow micro-mets	2	NO	YES	YES	YES
Powles et al.	1069/ multi-centered	Node neg & pos	2	YES	YES during Rx only	NO	YES
Saarto et al.	299/single institution	Node pos	3	NO	NO	NO	Decreased survival in clodronate arm

Modified from NSABP B-34 Protocol background

EFFECTS OF ADJUVANT CLODRONATE ON METASTASES AND MORTALITY IN 1,069 PATIENTS

	Clodronate	Placebo	Statistical Significance
Bone mets during total study period	63	80	HR 0.77 (95% CI 0.56-1.08) p = 0.127
Bone mets during medication period	12	28	HR 0.44 (95% CI 0.22-0.86) p = 0.016
Non-osseous mets	112	128	p = 0.257
Mortality	98	129	HR 0.77 (95% CI = 0.59-1.00) p = 0.047

"Conclusion: Adjuvant clodronate significantly reduces the incidence of bone metastases during the medication period and is associated with a significantly reduced mortality."

DERIVED FROM: Powles T et al. **Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer.** *J Clin Oncol* 2002;20(15):3219-3224.

SELECT PUBLICATIONS

Brown JE, Coleman RE. **The present and future role of bisphosphonates in the management of patients with breast cancer.** *Breast Cancer Res* 2002;4(1):24-29.

Chlebowski RT. **Factors influencing the role of bisphosphonates in breast cancer management.** *Semin Oncol* 2001;28(4 Suppl 11):42-48.

Diel IJ et al. **Reduction in new metastases in breast cancer with adjuvant clodronate treatment.** *N Engl J Med* 1998;339:357-363.

Diel IJ, Mundy GR. **Bisphosphonates in the adjuvant treatment of cancer: Experimental evidence and first clinical results. International Bone and Cancer Study Group (IBCG).** *British Journal of Cancer* 2000;82:1381-1386.

Pavlakis N, Stockler M. **Bisphosphonates for breast cancer.** *Cochrane Database Syst Rev* 2002;(1):CD003474.

Pickering LM, Mansi JL. **The role of bisphosphonates in breast cancer management: Review article.** *Curr Med Res Opin* 2002;18(5):284-295.

Powles T et al. **Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer.** *J Clin Oncol* 2002;20(15):3219-3224.

Saarto T et al. **Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial.** *J Clin Oncol* 2001; 19:10-17.

ADJUVANT BISPHOSPHONATES: RESEARCH BACKGROUND

In our trial, patients receiving clodronate had fewer subsequent bone and nonbone metastases. When we started our study ten years ago, we selected patients with tumor cells in the bone marrow, because we were convinced this was the best prognostic factor for bone metastases. Today we know it's a good prognostic factor for nonbone metastases, because it reflects the early hematogenous spread of breast cancer cells from the primary tumor.

The effect we observed on nonbone metastases could have been by chance since we only had 300 patients, which is a small number for an adjuvant trial. But we have a hypothesis that, perhaps, if you increase the amount of bisphosphonates on the bone surface, you may have an apoptotic effect on adjacent cells. We have evidence that these agents have this effect on osteoclasts and also have an anti-adhesive and anti-angiogenic effect.

The problem with the bisphosphonates is that the absorption rate is low, and in order to see an effect, you need a dose that may cause side effects, particularly on the gastrointestinal tract.

In comparison to cytotoxic substances, the rate of complications and side effects produced by the bisphosphonates is extremely low and is comparable to that observed for tamoxifen.

—Ingo Diel, MD

"Our results indicate that clodronate reduced the occurrence of bone metastases in patients with primary operable breast cancer, although this was only significant during the medication period. Furthermore, we have noted a significantly improved overall survival. These results need further evaluation by large clinical trials of adjuvant clodronate (such as the National Surgical Adjuvant Breast and Bowel Project B-34 trial, which has started accrual) and other bisphosphonates used for longer treatment periods to establish the clinical role of antiosteolytic bisphosphonate therapy for patients with primary operable breast cancer."

— Powles T et al. J Clin Oncol 2002;20(15):3219-3224

NSABP ADJUVANT CLODRONATE TRIAL

NSABP B-34 is evaluating adjuvant clodronate, an oral bisphosphonate, in women with node-negative and node-positive breast cancer. Data from Germany, as well as the Canadian and UK trial, demonstrate that clodronate reduces bone metastases and also improves survival. B-34 will randomize women to three years of clodronate or placebo. The choice of adjuvant therapy will be left to the investigator's discretion. We chose clodronate because it is the only bisphosphonate with data in the adjuvant setting.

If the B-34 results are positive, hopefully clodronate will be FDA-approved. In lieu of the ATAC trial results, it may be reasonable to combine an aromatase inhibitor with a bisphosphonate as adjuvant therapy.

Eventually, the NSABP plans to compare the bisphosphonates to find the best one. It may, however, be difficult to use an intravenous bisphosphonate in the adjuvant setting in terms of patient acceptability.

—Eleftherios Mamounas, MD