Adjuvant Bisphosphonates

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, and a new data set from Austria demonstrates that bone loss from anastrozole in women receiving an LHRH agonist is virtually completely prevented by the use of zolendronic acid.

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 Paterson, Chair. Tel: 403-994-1707
National Surgical Adjuvant Breast and Bowel Project

SOURCE: NCI Physician Data Query, February 2003.

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, February 2003.

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

Author	Reduction in skeletal mets	Reduction in nonskeletal mets	Survival advantage
Diel et al.	YES	YES	YES
Powles et al.	YES during Rx only	NO	YES
Saarto et al.	NO	NO	Decreased survival in clodronate arm

DERIVED FROM: NSABP B-34 Protocol background

ANASTROZOLE OR TAMOXIFEN IN COMBINATION WITH GOSERELIN (± ZOLEDRONIC ACID) AS ADJUVANT TREATMENT FOR HORMONE RECEPTOR-POSITIVE PREMENOPAUSAL BREAST CANCER – Open Protocol

Protocol ID: ABCSG-12

Eligibility	Premenopausal women with Stage I/II ER+/PR+ breast cancer, <10 positive lymph nodes
ARM 1	Surgery → goserelin + tamoxifen
ARM 2	Surgery → goserelin + tamoxifen + zoledronic acid
ARM 3	Surgery → goserelin + anastrozole
ARM 4	Surgery → goserelin + anastrozole + zoledronic acid

DERIVED FROM: Presentation, M Gnant, San Antonio Breast Cancer Symposium 2002.

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.

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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.

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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 10 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.

—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 anti-osteolytic 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

ZOLEDRONATE WITH GOSERELIN AND ANASTROZOLE OR TAMOXIFEN IN PREMENOPAUSAL WOMEN

"The preliminary analysis confirms that zoledronate is able to counteract bone mineral density deteriorations in premenopausal patients with hormone receptor-positive breast cancers treated with complete endocrine treatment with goserelin and tamoxifen or anastrozole. Without the bisphosphonates, bone mineral density deterioration is more pronounced in patients receiving goserelin + anastrozole than those receiving goserelin + tamoxifen. Longer-term bone mineral density monitoring will be necessary to determine whether these effects are prolonged."

—Gnant M, et al. Breast Cancer Res Treat 2002; Abstract 12.