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 actively being discussed is the combination of a bisphosphonate and an aromatase inhibitor, which would not only offer potential reduction in relapse rate but would mitigate bone loss. A data set from Austria presented at the 2002 and 2004 San Antonio Breast Cancer Symposia demonstrated that bone loss from anastrozole in premenopausal women receiving an LHRH agonist was prevented by the use of zoledronic acid.

PHASE III TRIALS OF ADJUVANT CLODRONATE FOR EARLY STAGE BREAST CANCER

Author	Reduction in skeletal metastases	Reduction in nonskeletal metastases	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.

ONGOING AND RECENTLY CLOSED ADJUVANT BISPHOSPHONATE TRIALS IN BREAST CANCER

Study	N	Randomization
NSABP-B-34 (Closed)	3,323	Clodronate qd x 3y Placebo qd x 3y
SHEFF-AZURE, BIG-1-04	3,300	Chemo and/or hormonal therapy + concurrent zoledronic acid q3-4wk x 6 → q3mo x 8 → q6mo x 5 Chemo and/or hormonal therapy alone
CALGB-79809	400	Zoledronate q3mo (months 1-24) + daily calcium + vitamin D (months 1-36) Daily calcium + vitamin D (months 1-36) + zoledronate q3mo (months 13-36)
CPMC-IRB-14069	120	Zoledronate q3mo x 4 + daily calcium + vitamin D Placebo q3mo x 4 + daily calcium + vitamin D
NCCTG-N02C1	220	(Oral risedronate qwk + daily calcium + vitamin D) x 1y (Oral placebo qwk + daily calcium + vitamin D) x 1y

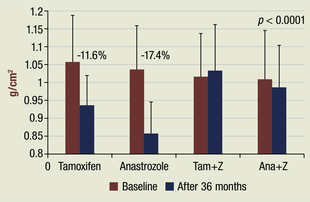
SOURCE: NCI Physician Data Query, January 2005.

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

Protocol ID: ABCSG-12 (Open)

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

CHANGES IN BONE MINERAL DENSITY OF THE LUMBAR SPINE (L1-L4) CAUSED BY ANASTROZOLE OR TAMOXIFEN IN COMBINATION WITH GOSERELIN (± ZOLEDRONIC ACID) IN ABCSG-12



Tam = tamoxifen; Z = zoledronic acid; Ana = anastrozole

SOURCE: Gnant M. Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 6.

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

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

Conclusion: Adjuvant clodronate may reduce the incidence of bone metastases during the medication period and is associated with a significant reduction in mortality.

DERIVED FROM: Powles T et al. *J Clin Oncol* 2002;20(15):3219-24.

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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(1):10-7.

Saarto T et al. **Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients.** *Proc ASCO* 2004;Abstract 527.

ADJUVANT BISPHOSPHONATES: RESEARCH BACKGROUND

In our trial, patients receiving clodronate had fewer subsequent bone and nonbone metastases. When we started our study, 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. We only had 300 patients, which is a small number for an adjuvant trial, so the effect we observed on nonbone metastases could have been by chance. We hypothesize that perhaps, if you increase the amount of bisphosphonates on the bone surface, you may have an apoptotic effect on adjacent cells. Evidence indicates that these agents have this effect on osteoclasts and also have an antiadhesive and antiangiogenic 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):3219-24.*

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 and the Canadian and UK trials demonstrate that clodronate reduces bone metastases and improves survival. B-34 randomly assigned women to three years of clodronate or placebo. The choice of adjuvant therapy was 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 — in terms of patient acceptability — to use an intravenous bisphosphonate in the adjuvant setting.

— Eleftherios P Mamounas, MD, MPH

BONE MINERAL DENSITY RESULTS FROM THE ADJUVANT TRIAL ABCSG-12

"From the results of this randomized trial [ABCSG-12] we conclude that cancer treatment-induced bone loss (CTIBL) is frequent in premenopausal patients receiving combination endocrine treatment. Severity of CTIBL increases with treatment duration. When anastrozole is used in combination with goserelin, CTIBL is significantly more severe than in the tamoxifen/goserelin group. Zoledronic Acid (4mg q6mo) can effectively counteract CTIBL in both settings."

— Gnant M. Presentation. San Antonio Breast Cancer Symposium, 2004.

NEW SWOG ADJUVANT BISPHOSPHONATE TRIAL

Within SWOG, we are about to start an adjuvant bisphosphonate trial that will follow up on the NSABP clodronate versus placebo trial. While we cannot predict the results of the NSABP's trial, we believe clodronate will be the winner. Our trial will compare adjuvant clodronate to a more potent oral bisphosphonate and an IV bisphosphonate. We want to see whether these agents can prevent bone metastases and impact disease-free and overall survival.

— Julie R Gralow, MD