**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 to 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.”


**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 compliance. This may be the case with zoledronic acid, which is to be FDA-approved. In lieu of the ATAC trial results, it may be reasonable to compare a bisphosphonate with data in the adjuvant setting with an aromatase inhibitor in the adjuvant setting. The adjuvant setting in terms of patient acceptance.

—Eleftherios Mamounas, MD

**Zoledronic with Goserelin and Anastrozole or Tamoxifen in Premenopausal Women**

“The preliminary analysis confirms that zoledronic acid 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.”


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**SELECT PUBLICATIONS**


**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 LH-RH 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 ID: 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 systemic therapy including tamoxifen at the investigator’s discretion.

**Study Contact:**

Alexandra Paterson, Chair. Tel: 403-994-1707

National Surgical Adjuvant Breast and Bowel Project

**SOURCE:** NCI Physician Data Query, February 2005.

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Reduction in metastatic mets</th>
<th>Reduction in nonmetastatic mets</th>
<th>Survival advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet et al.</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Powles et al.</td>
<td>YES during Rx only</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Saarto et al.</td>
<td>NO</td>
<td>NO</td>
<td>Decreased survival in clodronate arm</td>
</tr>
</tbody>
</table>

**DERIVED 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 | 0.0127 |
| Bone mets during medication period | 12 | 28 | 0.0951 |
| Non-osseous mets | 112 | 128 | 0.54 |
| Mortality | 98 | 129 | 0.007 |

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