CURRENT USE OF BISPHOPHONATES

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BISPHOSPHONATES FOR METASTATIC BREAST CANCER

- zoledronic acid 4 mg intravenously every 21-28 days
- De-escalate if stable disease
- Switch to oral ibandronate 50mg daily
- Escalate to Denosumab 120mg sct (RANK ligand inhibitor) if disease progresses beyond bisphosphonates
BONE DIRECTED THERAPY ALTERS BONE MICROENVIRONMENT

- Bisphosphonates embed in bone and induce apoptosis of activated osteoclasts in osteopoporosis

- Denosumab binds human RANK Ligand to inhibit bone resorption by osteoclasts thus decrease bone resorption
THE DISTRIBUTION OF SECONDARY GROWTHS IN CANCER OF THE BREAST.

BY STEPHEN PAGET, F.R.C.S.,
ASSISTANT SURGEON TO THE WEST LONDON HOSPITAL AND THE METROPOLITAN HOSPITAL.

An attempt is made in this paper to consider “metastasis” in malignant disease, and to show that the distribution of the secondary growths is not a matter of chance. It is urged both by Langenbeck and by Billroth that the question ought to be asked, and, if possible, answered “What is it that decides what organs shall suffer in a case of disseminated cancer?” If the remote organs in such case are all alike passive and, so to speak, helpless—all equally ready to receive and nourish any particle of the primary growth which may “slip through the lungs,” and
Bone is the most common site of breast cancer recurrence

There are fascinating interactions between tumours and their micro-environment (Paget’s 1889 Seed and Soil Hypothesis)

Bisphosphonates treat bone metastases in metastatic disease and prevent skeletal events

Can you prevent a seed embedding and growing by producing an unwelcoming soil
The Cancer Diaspora: Metastasis beyond the Seed and Soil Hypothesis

Kenneth J. Pienta, Bruce A. Robertson, Donald S. Coffey, and Russell S. Taichman

DOI: 10.1158/1078-0432.CCR-13-2158 Published November 2013

Abstract

Do cancer cells escape the confinement of their original habitat in the primary tumor or are they forced out by ecologic changes in their home niche? Describing metastasis in terms of a simple one-way migration of cells from the primary to the target organs is an insufficient concept to cover the nuances of cancer spread. A diaspora is the scattering of people away from an established homeland. To date, "diaspora" has been a uniquely human term used by social scientists; however, the application of the diaspora concept to metastasis may yield new biologic insights as well as therapeutic paradigms. The diaspora paradigm takes into account, and models, several variables including: the quality of the primary tumor microenvironment, the fitness of individual cancer cell migrants as well as migrant populations, the rate of bidirectional migration of cancer and host cells between cancer sites, and the quality of the target microenvironments to establish metastatic sites. Ecologic scientific principles can be applied to the cancer diaspora to develop new therapeutic strategies. For example, ecologic traps – habitats that lead to the extinction of a species – can be developed to attract cancer cells to a place where they can be better exposed to treatments or to cells of the immune system for improved antigen presentation. Merging the social science concept of diaspora with ecologic and population sciences concepts can inform the cancer field to understand the biology of tumorigenesis and metastasis and inspire new ideas for therapy. Clin Cancer Res; 19(21): 5849–55. ©2013 AACR.
The Cancer Diaspora
ADJUVANT BISPHOSPHONATES

- 2002
  - Trevor Powles Paterson S, et al:
  - Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. J Clin Oncol 20:3219-3224,

- 2006
Randomized, Placebo-Controlled Trial of Clodronate in Patients With Primary Operable Breast Cancer

Trevor Powles, Sandy Paterson, John A. Kanis, Eugene McCloskey, Sue Ashley, Alwynne Tidy...

Abstract

PURPOSE: The development of bone metastases depends on tumor-induced osteoclastic resorption of bone, which may be inhibited by the antosteolytic bisphosphonate clodronate. Given to patients with primary breast cancer, clodronate might reduce the subsequent incidence of bone metastases.

PATIENTS AND METHODS: This double-blind, multicenter trial accrued 1,069 assessable patients with operable breast cancer between 1989 and 1995. All patients received surgery, radiotherapy, chemotherapy, and tamoxifen as required. Patients were randomized to receive oral clodronate 1,600 mg/d or a placebo for 2 years starting within 6 months of primary treatment. The primary end point was relapse in bone, analyzed on an intent-to-treat basis, during the medication period and during the total follow-up period (median follow-up, 2,007 days). Secondary end points were relapse in other sites, mortality, and toxicity.

RESULTS: During the total follow-up period, there was a nonsignificant reduction in occurrence of bone metastases (clodronate, n = 63; placebo, n = 80; hazards ratio [HR], 0.77; 95% confidence interval [CI], 0.56 to 1.08; P = .127). During the medication period there was a significant reduction in the occurrence of bone metastases (clodronate, n = 12; placebo, n = 28; HR, 0.44; 95% CI, 0.22 to 0.86; P = .016). The occurrence of nonosseous metastases was similar (clodronate, n = 112; placebo, n = 128; P = .257), but there was a significant reduction in mortality (clodronate, n = 98; placebo, n = 129; P = .047) during the total follow-up period.

CONCLUSION: Clodronate, given to patients with primary operable breast cancer, may reduce the occurrence of bone metastases, although this reduction was only significant during this medication period. There was a significant reduction in mortality.

Background: The bisphosphonate clodronate (Bonefos) may reduce the incidence of bone metastases by inhibiting tumor-induced osteoclastic resorption of bone.

Methods: This randomized, double-blind, placebo-controlled, multicenter trial evaluated the efficacy and safety of oral clodronate in 1,069 patients with primary operable stage I-III breast cancer from 1989–2000. Patients received oral clodronate (1600 mg/day) or placebo for 2 years, starting within 6 months of primary treatment (surgery, radiotherapy, and tamoxifen). Ad hoc analyses from this study have been published previously (Powles et al. JCO 2002), and the unpublished protocol-specified results and ad hoc analysis of stage II/III patients are reported here. The protocol-specified primary endpoint was time to first bone metastasis during the 5-year study period. The secondary endpoint was overall survival. These endpoints were analyzed by unstratified Log-rank test and hazard ratio (HR) with 95% CI. Results: Patient demographics were similar between treatment groups. Oral clodronate significantly reduced the risk of bone metastases by 45% in all patients during the medication period (2 years: HR = 0.546, P = 0.031), and by 31% during the study period (5 years: HR = 0.692, P = 0.043) compared to placebo. Similarly, clodronate significantly reduced the risk of bone metastases in patients with stage II/III disease during the medication (2 years: 50%, HR = 0.496, P = 0.020) and study (5 years: 41%, HR = 0.592, P = 0.009) periods. Oral clodronate vs. placebo significantly improved overall survival (23% reduction in risk of death: HR = 0.768, P = 0.048) and survival for stage II/III patients (26% reduction in risk of death: HR = 0.743, P = 0.041). Oral clodronate was well tolerated, with mild-to-moderate diarrhea being the most frequently reported adverse event. Conclusion: In patients with primary operable breast cancer, oral clodronate significantly reduced the risk of bone metastases and significantly improved survival rates during the medication and 5-year study periods compared to placebo. Similar results were seen in stage II/III patients.
ASCO plenary presentation of Austrian ABCSG-12 study documenting a disease-free survival advantage with adjuvant zoledronate (ZDA) in premenopausal women with ER-positive breast cancer (M Gnant)

‘hold off’ on using bisphosphonates outside a protocol setting and to wait until another major trial, the AZURE study is reported.
Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer. The AZURE Trial (BIG 01/04) ‘hold off’ on using bisphosphonates outside a protocol setting and to wait until another major trial, the AZURE study is reported.

Coleman RE et al.

*Proc SABCS 2010;Abstract S4-5.*
Stage II to III, node-positive breast cancer with a completed primary resection

Eligibility (N = 3,360)

Standard therapy

Standard therapy + Zoledronic acid (ZOL)* 4 mg x 5 yrs

* Months 0-6, 6 doses q3-4 wks; Months 7 to 30, 8 doses q3 mos; Months 31 to 60, 5 doses, q6 mos

Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.
The adjuvant use of zoledronic acid did not improve DFS in this population of patients with stage II/III breast cancer (DFS, $P = 0.79$; IDFS, $P = 0.73$).

A subgroup analysis of post-menopausal (>5 years) patients and those aged >60 years showed significant differences in OS between the control and zoledronic acid groups.

- 120 vs 86 deaths ($P = 0.017$)

The adjuvant use of bisphosphonates appears to be dependent on a low estrogen/inhibin concentration within the bone microenvironment.

The AZURE data are strikingly different than those observed in the ABCSG XII trial.

Investigator Commentary: AZURE Adjuvant Bisphosphonate Study

In the AZURE trial, no improvement in disease-free survival was evident for patients who received the adjuvant bisphosphonate versus those who did not, with a hazard ratio of 0.98. An interesting and exploratory subset analysis that can only be viewed as hypothesis generating was conducted to determine why these results are so discrepant from the results of ABCSG-12. This analysis suggests that a benefit may actually be present for women who are menopausal or in a low-estrogen setting. The findings for this subset would be consistent with the observed benefit of zoledronic acid (ZA) in the younger patients enrolled in ABCSG-12, who were premenopausal but received goserelin with either tamoxifen or an aromatase inhibitor. However, this explanation is hypothetical and is not clinically actionable, except perhaps to inform yet another clinical trial.

Commentary by Clifford Hudis, MD, December 11, 2010

AZURE was a larger study and included a broader range of patients with breast cancer than were enrolled in ABCSG-12, and there was absolutely no suggestion of an improvement in disease-free or overall survival. This was clearly a negative result and implies that clinicians should not be offering adjuvant ZA with the expectation of preventing cancer recurrence.

Interview with Harold J Burstein, MD, PhD, December 22, 2010
Effects Of Bisphosphonate Treatment On Recurrence And Cause-specific Mortality In Women With Early Breast Cancer: A Meta-analysis Of Individual Patient Data From Randomised Trials


Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)’s Bisphosphonate Working Group.
Breast Cancer Recurrence: All Women

All Recurrences

- 17709 women
- 3408 events

- Recurrence rates (% / year) and logrank analyses:
  - Allocation: Bisph, Not
  - Years 0 – 4: 3.88 (1382 / 37591), 2.43 (319 / 13112), 1.04 (18 / 1730)
  - Years 5 – 9: 2.31 (1135 / 38174), 1.03 (264 / 13699), 0.68 (17 / 1946)

- Not 26.5%
- Bisph 25.4%
- 10-y gain 1.1% (SE 0.9)
- Logrank 2p = 0.08

Distant recurrences

- 17709 women
- 2835 events

- Distant recurrence rates (% / year) and logrank analyses:
  - Allocation: Bisph, Not
  - Years 0 – 4: 2.97 (1135 / 38174), 1.93 (264 / 13699), 0.68 (17 / 1946)

- Not 22.3%
- Bisph 20.9%
- 10-y gain 1.4% (SE 0.9)
- Logrank 2p = 0.03
Differential response by menopausal status

Breast Cancer Recurrence: Postmenopausal Women*

Cancer Therapy and Research Center at UT Health Science Center

* Includes induced menopause and women aged >55 if unknown

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Differential response by menopausal status

Cancer Therapy and Research Center at UT Health Science Center

**Bone Recurrence By Menopausal Status**

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Women Allocated Bisph</th>
<th>Allocated Not</th>
<th>Bisph events Logrank Variance of O-E</th>
<th>Ratio of annual event rates Bisph : Not</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-menopausal <strong>†</strong></td>
<td>170/3134 (5.4%)</td>
<td>163/2711 (6.0%)</td>
<td>-5.3 75.0</td>
<td>0.93 (SE 0.11)</td>
</tr>
<tr>
<td>Peri-menopausal *</td>
<td>28/461 (6.1%)</td>
<td>19/367 (5.2%)</td>
<td>2.0 8.8</td>
<td></td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>222/5737 (3.9%)</td>
<td>286/5299 (5.4%)</td>
<td>-47.8 115.7</td>
<td>0.66 (SE 0.08)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>420/9332 (4.5%)</strong></td>
<td><strong>468/8377 (5.6%)</strong></td>
<td><strong>-51.1 199.6</strong></td>
<td><strong>0.774 (SE 0.062)</strong></td>
</tr>
</tbody>
</table>

- 99% or ± 95% confidence intervals
- Heterogeneity between 3 categories: $\chi^2 = 7.5; p = 0.02$
- **†** includes women aged < 45 if unknown
- * Includes women aged 45-55 if menopausal status unknown

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# Breast Cancer Mortality By Menopausal Status

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Women Allocated Bisph</th>
<th>Events/Women Allocated Not</th>
<th>Bisph events Logrank Variance</th>
<th>Ratio of annual event rates Bisph : Not</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-menopausal</td>
<td>445/3134 (14.2%)</td>
<td>426/2711 (15.7%)</td>
<td>-0.2 186.5</td>
<td>1.00 (SE 0.07)</td>
</tr>
<tr>
<td>Peri-menopausal</td>
<td>42/461 (9.1%)</td>
<td>38/367 (10.4%)</td>
<td>-0.6 15.1</td>
<td></td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>544/5737 (9.5%)</td>
<td>602/5299 (11.4%)</td>
<td>-45.2 241.8</td>
<td>0.83 (SE 0.06)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1031/9332 (11.0%)</td>
<td>1066/8377 (12.7%)</td>
<td>-45.9 443.4</td>
<td>0.902 (SE 0.04) 2p = 0.03</td>
</tr>
</tbody>
</table>

- 99% or <-> 95% confidence intervals

Heterogeneity between 3 categories: $\chi^2 = 3.7; p > 0.1; NS$

- Bisph better
- Not better

Treatment effect $2p = 0.03$
Test for trend: $\chi^2 = 3.7; 2p = 0.06$
Conclusions

- Adjuvant bisphosphonates reduce bone metastases and improve survival in post-menopausal women.
  - 34% reduction in risk of bone recurrence ($p=0.00001$).
  - 17% reduction in risk of breast cancer death ($p=0.004$).
  - No significant reduction in first distant recurrence outside bone.
  - Risk reductions similar irrespective of ER, node status, use/non use of chemotherapy.
  - Benefits similar for aminobisphosphonates and clodronate.

- No effects apparent on disease outcomes in pre-menopausal women.

- No significant effects on non breast cancer deaths, contralateral breast cancer or loco-regional recurrence.
ADJUVANT BISPHOSPHONATES IN EARLY BREAST CANCER: CONSENSUS GUIDANCE FOR CLINICAL PRACTICE FROM A EUROPEAN PANEL

Ann Oncol March 2016

Bisphosphonates should be considered as part of routine clinical practice for the prevention of treatment induced bone loss in all patients with a T score of $<-2.0$ or $\geq 2$ clinical risk factors for fracture.

Evidence from a meta-analysis of trial data of $>18,000$ patients supports clinically significant benefits of bisphosphonates on the development of bone metastases and breast cancer mortality in post-menopausal women or those receiving ovarian suppression therapy.

Bisphosphonates (either intravenous zoledronic acid or oral clodronate) are considered as part of the adjuvant breast cancer treatment in this population and the potential benefits and risks discussed with relevant patients.
Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline

Sukhinder Dhesy-Thind, Glenn G. Fletcher, Phillip S. Blanchette, Mark J. Clemons, Melissa S. Dillmon, Elizabeth S. Frank, Sonal Gandhi, Rasna Gupta, Mihaela Mates, Beverly Moy, Ted Vandenbarg, and Catherine H. Van Poznak

ABSTRACT

Purpose
To make recommendations regarding the use of bisphosphonates and other bone-modifying agents as adjuvant therapy for patients with breast cancer.

Methods
Cancer Care Ontario and ASCO convened a Working Group and Expert Panel to develop evidence-based recommendations informed by a systematic review of the literature.

Results
Adjuvant bisphosphonates were found to reduce bone recurrence and improve survival in postmenopausal patients with nonmetastatic breast cancer. In this guideline, postmenopausal includes patients with natural menopause or that induced by ovarian suppression or ablation. Absolute benefit is greater in patients who are at higher risk of recurrence, and almost all trials were conducted in patients who also received systemic therapy. Most studies evaluated zoledronic acid or clodronate, and data are extremely limited for other bisphosphonates. While denosumab was found to reduce fractures, long-term survival data are still required.

Recommendations
It is recommended that, if available, zoledronic acid (4 mg intravenously every 6 months) or clodronate (1,600 mg/d orally) be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy. Further research comparing different bone-modifying agents, doses, dosing intervals, and durations is required. Risk factors for osteonecrosis of the jaw and renal impairment should be assessed, and any pending dental or oral health problems should be dealt with prior to starting treatment. Data for adjuvant denosumab look promising but are currently insufficient to make any recommendation. Use of these agents to reduce fragility fractures in patients with low bone mineral density is beyond the scope of the guideline. Recommendations are not meant to restrict such use of bone-modifying agents in these situations.
ADJUVANT BISPHOSPHONATES

- Zoledronic acid (4 mg intravenously every 6 months) or clodronate (1,600 mg/d orally) be considered as adjuvant therapy for postmenopausal patients with breast cancer.

- Further research comparing different bone-modifying agents, doses, dosing intervals, and durations is required.

- Risk factors for osteonecrosis of the jaw and renal impairment should be assessed.

- Data for adjuvant denosumab look promising but are currently insufficient to make any recommendation.
TOXICITY OF IV ADJUVANT BISPHOSPHONATES

- ONJ: 0.6-1.5-2.1% (3% bone metastases)
  - Dependent on both dose and duration
- Renal
  - Common effects if administered intravenously high concentrations and fast injection or Cr Cl < 60mL/min
- Acute Phase reaction
  - Transient 30% upwards fever fatigue myalgia arthralgia bone pain vertigo uveitis episcleritis (very rare)
- Atypica femoral #
TOXICITY OF ADJUVANT BISPHOSPHONATES

http://www.scottetreoutdds.com/uncategorized/osteonecrosis-jaw
Figure 1 Anterior segment photographs at initial onset of anterior uveitis.
Notes: (A) At initial onset, hypopyon with hemorrhage and minute granulomatous keratic precipitates, in the anterior chamber, are observed. (B) During anterior chamber lavage in vitrectomy, the hypopyon appears to have high viscosity.

Authors Sato T, Minakuchi S, Mochizuki M, Takeuchi M
Clinical Ophthalmology. 8 January 2014 Vol 2014:8 187-190
TOXICITY OF ORAL ADJUVANT BISPHOSPHONATES

- Oral administration has low absorption (<,5%) thus high doses are required
- ONJ: 0.6-1.5-2.1% (3% bone metastases)
  - Dependent on both dose and duration
- Renal
  - common effects if administered intravenously high concentrations and fast injection or Cr Cl < 60mL/min
- Atypica femoral #
- Oesophagitis / gastritis orally /n v d
- Strict guidelines regarding empty stomach , no bending
- Clodronate is enormous
- 2 hour window from calcium
- Compliance and concordance
ADJUVANT BISPHOSPHONATES

- SWOGS0307. - compared 3 years clodronate versus ibandronate versus zoledronic acid
- No placebo or no bisphosphonate arm
- Metastatic cancer doses (high daily oral administration)
- Data monitoring committee recommended early reporting as there was no realistic chance of statistically significant difference.
- No differences in 5-year disease free survival (DFS; 87% to 88%), overall survival (OS; 93%), or fractures.
- No differences on the basis of age or menopausal status.
- Small differences in grade 3 to 4 events (10.5% ibandronate, 8.3% clodronate, 8.8% zoledronic acid) and osteonecrosis of the jaw (ONJ; 0.6% ibandronate, 0.3% clodronate, 1.2% zoledronic acid).
ADJUVANT BISPHOSPHONATES

- Current Practical Solution
- Dental review
- Risk assessed as sufficiently high to receive chemotherapy then bisphosphonates automatically considered
- 3-6 cycles zometa delivered with chemotherapy (adjuvant or neo-adjuvantly)
- Continue zometa every 6 months if attending day unit for trastuzumab
- Endocrine therapy introduced first
- Oral ibandronate daily commenced up to six months after most recent zometa (once patient confirmed to be tolerating endocrine therapy).
- Upon discharge from Oncology clinic GP takes over bisphosphonate prescription in the community
- If patient referred back and not tolerating oral daily can consider weekly ibandronate 150mg or alendronate 70mg
Consider bisphosphonates as part of routine clinical practice for the prevention of treatment induced bone loss in all patients with a T score of $\leq -2.0$ or $\geq 2$ clinical risk factors for fracture.

Meta-analysis of trial data of $>18,000$ patients supports clinically significant benefits of bisphosphonates on the development of bone metastases and breast cancer mortality in post-menopausal women or those receiving ovarian suppression therapy.

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ADJUVANT BISPHOSPHONATES

- Dental review
- Menopausal status
- Risk assessed as sufficiently high to benefit
- Overlapping benefit if bones already at risk
THANK YOU