Targeting the osteoclast in early stage breast cancer

Cancer to bone: a fatal attraction!

Wilbaecher, Guise, McCauley
Nat Rev Ca 2011; 11:411

Thank you Dr Julie Gralow, for sharing some slides & thoughts

What are my targets for this lecture?

• What is the bone microenvironment (BM)?
• Why is the BM important in early breast ca?
• How does tumor hijack the bone marrow?
• What is the mechanism of action of the available anti-osteoclast agents
• How does menopause affect BM?
• What are the key clinical trials data of adjuvant anti-osteoclast trials?
• What recent hypotheses have emerged
• What trials are ongoing?

What is the normal bone microenvironment?

2 main cell types & bone matrix

Osteoclast (Heme Stem Cell)
Osteoblast (Mesenchymal SC)
Osteomacs (tissue mac)

10% of the skeleton is replaced each year!

Wilbaecher KN, Guise TA. Nat Rev Ca 2011; 11:411
What is origin of 2 main bone cell types? Heme stem cell, Mesenchymal Stem Cell

Why is the bone microenvironment so important? 3 reasons

• Premetastatic niche
• Tumor sanctuary: micromets “home” to BM
• Incubator for drug resistance

Why is bone so important? Bone marrow (BM) microenvironment is: 1) premetastatic niche

• Premetastatic niche: distant sites “primed” by tumor-secreted cytokines that hijack normal cells:
  – Hematopoetic Stem Cells (HSCs): VEGFR-1+
  – Endothelial Stem Cells (ESCs): VEGFR-2+
  – Stromal cells (TAFs): Tumor Activated Fibroblasts
  – Inflammatory cells (TAMs): Tumor Associated Macrophages
• Induce angiogenesis, fibronectin (scaffolding to adhere)

Wilson C.  Cancer Treat Rev 2012; 38:877
Kaplan RN.  Cancer Res 2006; 66:11089
Why is bone so important? Bone marrow (BM) microenvironment is: 2) tumor sanctuary

- Tumor cell expresses CXCR4 receptor
- BM $\rightarrow$ SDF1 (aka CXCL12) the cognate ligand
  - Think cocaine craving here!
- CXCR4 positive tumor cells migrate to BM
- CXCR7 receptor: survival by glue to BM stroma
  - VLA-4: tumor glue to ECM (fibronectin & collagen)
  - Think Ulysses lashed to the mast during gale
  - “Environmentally mediated” EM-DR
  - “Cell adhesion mediated” CAM-DR
  - Adhesion-mediated quiescence protects from cytotoxics which target dividing cells

Meads MB. Clin Cancer Res 2008;14:2519

Why is Bone Marrow (BM) microenvironment so important: 3) contributor to drug resistance (DR)

- Compare resistance in tumor cell cultures treated with cytotoxics based on interaction with microenvironment (adhesion) or not (suspension)
  - adhesion model: de novo resistance 2X $>$ suspension
  - When these cells exposed to cytotoxics without adhesion, had acquired drug resistance
- NOW...Think what happens w/ adjuvant chemo
- If tumor cells migrate to bone and “adhere”:
  - 1) protected “CAM-DR” “EM-DR”
  - 2) selected for drug resistance: acquired

Meads MB. Clin Cancer Res 2008;14:2519
How does the tumor hijack the BM to survive?
This is the “vicious cycle”

- Tumor cells disrupt normal bone homeostasis
- Produces growth factors and cytokines
- Tumor PTHrP \( \uparrow \) RANK ligand from OB & stroma
- Uncouples bone remodeling: \( \uparrow \) osteoclast bone resorption & and \( \downarrow \) osteoblast bone formation
- Stroma less adhesive so tumor cells can migrate

Meads MB. Clin Cancer Res 2008;14:2519

Hijacking normal bone remodeling & resorption allows to tumor persist & grow in bone

Sterling JA. Bone 2011; 48:6-15

How does the bone microenvironment change with menopause? \( \uparrow \uparrow \) Turnover and “at risk”

Menopause Affects Bone Cell Function and Bone Derived Growth Factors

5 – 10 years

PREMENOPAUSAL
- Osteoclastic
- Cycling estrogen
- Local activity, BMP

PERI-MENOPAUSAL
- Osteoclastic
- Cycling estrogen
- Activin, BMP tone

POSTMENOPAUSAL
- Osteoclastic
- Activin, BMP tone

Coleman R. ASCO 2012 #502
It’s not only about estrogen! What else affects the bone microenvironment and what changes with menopause?

Wilson C. Cancer Treat Rev 2012; 38:877

Osteoporosis

- Osteoporosis is characterized by decreased bone mineral density.
- The increased bone resorption associated with osteoporosis may provide fertile “soil” for cancer growth.

Lipton A. ASCO 2012 #501

So, why target the osteoclast?

- Maintain skeletal integrity (bone density)
- Prevent “hijacking” by tumor and drug-resistant recurrences

What agents do we have
What have the clinical trials shown?
What agents are available? Bisphosphonates, RANK ligand inhibitor

What have clinical trials taught us?

• Cochrane Overview 3-2012
• Original Clodronate Studies
• Zoledronic Acid Studies: ABCSG, AZURE
• ASCO abstracts: new hypothesis
What does the Cochrane meta-analysis show? Bisphosphonates: no bone metastases vs control in Early Breast Cancer (EBC)

Bisphosphonates:
- Early versus delayed: no bone metastases vs control in Early Breast Cancer (EBC)

Comparison of Adjuvant Breast Cancer Trials of Clodronate vs. Placebo/Control

<table>
<thead>
<tr>
<th></th>
<th>NSABP B-34</th>
<th>Powles</th>
<th>Diel</th>
<th>Saarto</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>3323</td>
<td>1069</td>
<td>290</td>
<td>299</td>
</tr>
<tr>
<td>Treatment site</td>
<td>Multi-center</td>
<td>Multi-center</td>
<td>Single institution</td>
<td>Single institution</td>
</tr>
<tr>
<td>Selection</td>
<td>Stage I-II</td>
<td>Stage I-III</td>
<td>BM+</td>
<td>LN+</td>
</tr>
<tr>
<td>Treatment length (y)</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Control arm</td>
<td>placebo</td>
<td>placebo</td>
<td>observation</td>
<td>observation</td>
</tr>
<tr>
<td>Follow-up time (y)</td>
<td>8.4</td>
<td>10</td>
<td>8.5</td>
<td>10</td>
</tr>
<tr>
<td>bone mets?</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>OS benefit?</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

Oral Clodronate for Adjuvant Treatment of Breast Cancer

Powles T. Breast Cancer Res 2006; 8:R13

N = 1069 patients, primary breast cancer

At 2 yrs, HR: 0.546 (P = .031)
At 5 yrs, HR: 0.692 (P = .043)

Clodronate (n = 530)
Placebo (n = 539)

NSABP B-34: Adjuvant Clodronate Analysis of Specified Endpoints
Paterson A et al, SABCS 2011, Abstract 52-3

<table>
<thead>
<tr>
<th>End-point</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>Clod (n = 1662)</td>
<td>0.913 (0.778-1.072)</td>
<td>.266</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 1661)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>Clod (n = 1662)</td>
<td>0.642 (0.567-1.054)</td>
<td>.131</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 1661)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFI</td>
<td>Clod (n = 1662)</td>
<td>0.634 (0.567-1.038)</td>
<td>.101</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 1661)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMFI</td>
<td>Clod (n = 1662)</td>
<td>0.765 (0.548-1.068)</td>
<td>.114</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 1661)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBMF</td>
<td>Clod (n = 1662)</td>
<td>0.743 (0.554-0.996)</td>
<td>.046</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 1661)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- For all endpoints, a trend towards less events in clodronate arm
- Was this study underpowered based on patient selection, # events, potency of chosen bisphosphonate?

Comparison of Adjuvant Breast Cancer Trials of Zoledronic Acid vs Control vs Timing

<table>
<thead>
<tr>
<th></th>
<th>AZURE ZA v nil</th>
<th>ABCSG-12 ZA vs nil</th>
<th>ZO-FAST Now v Later</th>
<th>Z-FAST Now v Later</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>3360</td>
<td>1803</td>
<td>1060</td>
<td>602</td>
</tr>
<tr>
<td>Stage</td>
<td>II-III</td>
<td>I-II</td>
<td>I-IIa</td>
<td>I-IIa</td>
</tr>
<tr>
<td>Dur’n ZA</td>
<td>5 yr</td>
<td>3 yr</td>
<td>5 yr</td>
<td>5 yr</td>
</tr>
<tr>
<td>Total ZA doses</td>
<td>19</td>
<td>6</td>
<td>10 (max)</td>
<td>10 (max)</td>
</tr>
<tr>
<td>Chemo</td>
<td>95%</td>
<td>5%</td>
<td>51%</td>
<td>50%</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Pre &amp; Post</td>
<td>Pre plus goserelin</td>
<td>Post</td>
<td>Post</td>
</tr>
<tr>
<td>DFS?</td>
<td>N0</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>OS?</td>
<td>N0</td>
<td>YES</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

Positive trials: All ER-pos, less chemo; all ovarian suppression
What did ABCSG-12 show @ 62 mo?

Eligible: premen; stage I-II, ER or PR pos. N=1803 (7 yr)

1o Aim: DFS effect of ZOL


Node + ~ 30%
Node - ~ 66%
Age ≤40 ~ 22%
Age >40 ~ 80%

Zoledronic acid 4 mg IV Q6 mo x 3 yr
• No benefit <40y
• “carry over” DFS benefit 2 yrs after stop ZOL

Targeting Bone to Cure Breast Cancer: Should we believe? NOT YET!

Gabriel N Hortobagyi

• #501 MA.27: Effect of osteoporosis in postmenopausal women randomized to adjuvant exemestane or anastrazole. Alan Lipton
  • Pts who got osteoporosis rx had EFS
• #502 AZURE-BIG 01/04: The influence of menopausal status (supercedes) age on treatment effects. Robert E Coleman
  • Post menopausal pts had modest benefit
  • Pre-, peri-menopausal pts MAY have detriment!

#501: Effect of osteoporosis in MA.27

Hypothesis:
A) Does “pt-reported osteoporosis (OP) affect: Event Free Survival EFS or Distant Disease Free Survival DDFS?
B) Does OP treatment (OPT) affect EFS

MA.27: N=7576, postmenop; T1= 72%; N0 71%; ACT 31%
OP Dx: 17% (1294); OPT: 36% (2711: 1101 dx OP & 1610 no osteoporosis but had OPT;)

Anastrozole vs Exemestane EFS

Alan Lipton
**EFS by Osteoporosis Therapy**

**LIMITATIONS**
- Self-reported; retrospect

**CONCLUSIONS**
- OPT significantly improves EFS, DDFS
- May improve outcome of adjuvant AI therapy
- Need more trials

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**Interpretation and Conclusions**

- While breast cancer is less frequent in patients with OP, it might have improved outcome, with or without OPT
- Is this related to “natural” estrogen deprivation?
- OPT, with/without OP might improve outcomes of breast cancer treatment
- Is this a result of bisphosphonate therapy, raloxifene or both?
- This study might provide indirect support for the beneficial effects of bisphosphonates in the management of ER+ postmenopausal early breast cancer
- OPT when OP is present in patients with breast cancer is a no brainer! OPT without OP requires stronger evidence. GN Hortobagyi, MDACC, ASCO 2012

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**#502: Adjuvant Zoledronic Acid Therapy in Early Breast Cancer (AZURE – BIG 01/04): Age, not menopausal status explains results RE Coleman**

This report: Show results by Menopausal status, i.e 2o aims

**AZURE Study Aims:**
- 1o Aim DFS: This was completely identical.

**NEGATIVE STUDY**
- 2o Prespecified subgroup analysis: Included
  a) Menopausal status: Premen, Peri (<5 yrs post men), Established menopausal (≥ 5 yr), Unknown; b) ER status
#502 Coleman AZURE: Conclusions on Role of Adjuvant Zoledronic Acid in Early Breast Cancer

1) No overall benefit in unselected population
2) Significant benefit in pts with established menopause
3) Worse in PRE- & PERIMENOPAUSAL women
4) No decrease in bone recurrence in any group
5) Multiple data sets support role in POST-MEN pts: DrGN Hortobagyi, Discussant, disagrees

Variable Efficacy in an Unselected Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall DFS result</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZURE</td>
<td>0.98 (0.85, 1.13)</td>
<td>.79</td>
</tr>
<tr>
<td>ABCSG XII</td>
<td>0.71 (0.55, 0.92)</td>
<td>.013</td>
</tr>
<tr>
<td>ZO-FAST</td>
<td>0.68 (0.44, 0.97)</td>
<td>.04</td>
</tr>
<tr>
<td>NSABP-B34</td>
<td>0.91 (0.79, 1.07)</td>
<td>.27</td>
</tr>
<tr>
<td>GAIN</td>
<td>0.95 (0.77, 1.15)</td>
<td>.59</td>
</tr>
<tr>
<td>Z-FAST</td>
<td>0.79 (0.46, 1.33)</td>
<td>.42</td>
</tr>
<tr>
<td>E-ZO-FAST</td>
<td>1.74 (0.83, 3.67)</td>
<td>.14</td>
</tr>
</tbody>
</table>

- Dr Coleman presented this as evidence of a trend, with one exception, E-ZO-FAST, “small”
- Dr Hortobagyi contends: too heterogeneous to combine

What mechanism may explain why AZURE post-menopausal pts had benefit but premen pts did worse?
Estrogen (E2) antagonizes Zoledronic Acid (ZA)!

Steinman RA. Breast Cancer Res 2012; 14:213
Dr Hortobagyi’s Interpretation

- Evidence appears to be accumulating in support of the use of adjuvant bisphosphonates in postmenopausal patients with ER+ early breast cancer.
- However, AZURE (like most other, similarly designed studies) did not meet its primary endpoint. The analyses presented today are exploratory and hypothesis-generating.
- The other ZA studies presented in tabular summaries and Hazard Ratios are quite heterogeneous in design, size, patient population, endpoints and definitions of menopausal status.
- Review abstracts 513 and 548.

Questions

- Why is apparent benefit limited to non-osseous metastases?
- How are estrogen levels associated with bisphosphonate effects? Or are they?
- If most of the bone loss of menopause occurs during the first five years, why would the “benefit” be seen only after that time? How menopausal do patients need to be to benefit?
- Does ovarian suppression with an LHRH agonist provide an endocrine environment similar to that found >5 years after natural menopause, but not earlier?
- Do we need to revisit the basic hypothesis on which this trial was developed?
- Is bone just a red herring in these studies?

Conclusions

- Osteoporosis and osteoporosis therapy were associated with improved EFS and DDFS.
- We should treat OP as indicated by current guidelines!
- Subset analyses of multiple prospective RCTs (and two meta analyses) suggest that adjuvant bisphosphonates might reduce risk of recurrence for some postmenopausal patients with ER+ early breast cancer.
- Confirmatory prospective trials will provide the evidence needed to incorporate bisphosphonates in standard adjuvant regimens.
- Until then, these results are a note of caution!
Do Bisphosphonates have antitumor efficacy? Two tantalizing studies suggest so.

- WHI study
- Preoperative chemotherapy subset of AZURE

How did bisphosphonate use affect incidence of invasive BC in Women’s Health Initiative (WHI)?

- **AIM:** do ORAL BPs also inhibit BC incidence
- **PTS:** 154,768 postmen women, WHI cohort
  - Hip fracture risk score used to adjust for potential BMD difference between BP users and non-users
- **BPs:** Alendronate (90%), etidronate (10%)
- **RESULT:** 32% reduction in ER pos only

Chlebowski RT. J Clin Oncol 2010;22:3582

Are bisphosphonates (BP) preventive agents?

<table>
<thead>
<tr>
<th>Rate per 1000 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Invasive BC</td>
</tr>
<tr>
<td>ER pos</td>
</tr>
<tr>
<td>ER neg</td>
</tr>
<tr>
<td>In Situ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ 32%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>↓ 30%</td>
<td>0.002</td>
</tr>
<tr>
<td>↑ 34%</td>
<td>0.27</td>
</tr>
<tr>
<td>↑ 59%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Adjusted for age, ethnicity, smoking, alcohol use, physical activity, mammogram in the last 2 years, prior hormone use, total calcium, total vitamin D, 5 year hip fracture risk, and Gail 5 year breast cancer risk and stratified on WHI trial randomization arm.

Chlebowski RT. J Clin Oncol 2010;22:3582
Is there evidence for direct anti-tumor effect of BP? Preoperative Chemotherapy +/- Zoledronic Acid in the AZURE Trial

- Retrospective, exploratory analysis
- AZURE trial subset: 205 preop chemo pts

**Results:**

<table>
<thead>
<tr>
<th>No of pts</th>
<th>Chemo +ZA Chemo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>101</td>
<td>104</td>
<td>0.002</td>
</tr>
<tr>
<td>Residual inv.</td>
<td>28.2</td>
<td>42.4</td>
</tr>
<tr>
<td>tumor, mm (adj)</td>
<td>10.9%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

**Conclusion:** Possible direct anti-tumor effect of zoledronic acid

Coleman RE. Br J Cancer 2010; 102 102

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**What trials are addressing clinical questions?**

- Duration & frequency of treatment?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Prior Bisphos</th>
<th>Dose Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTIMIZE2</td>
<td>ZOL x 10-15 mo</td>
<td>Q1 v 3 mo</td>
</tr>
<tr>
<td>BISMARK</td>
<td>ZOL x 4-5+ rx</td>
<td>Q4 wk v BTO*</td>
</tr>
<tr>
<td>CALGB 70604</td>
<td>None</td>
<td>Q1 v 3 mo</td>
</tr>
<tr>
<td></td>
<td>Anti-tumor activity?</td>
<td>Coleman R JNCI 2012</td>
</tr>
<tr>
<td>SWOG 0307</td>
<td>Adj St I-II</td>
<td>ZOL v CLO v IBAN</td>
</tr>
<tr>
<td>NATAN</td>
<td>NACT St II-III</td>
<td>ZOL v Placebo</td>
</tr>
<tr>
<td>D-CARE</td>
<td>Adj &amp; NACT</td>
<td>DEN 120 v PI</td>
</tr>
<tr>
<td>MDACC</td>
<td>Ph I/II-MBC</td>
<td>DASAT w ZOL</td>
</tr>
<tr>
<td>ABCSG-18</td>
<td>Adj AI</td>
<td>DEN 60 v Plcb</td>
</tr>
</tbody>
</table>

Fornier MN. JCO 2010; 12:5127; *Bone TurnOver

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**Did I hit my targets for this lecture?**

- The bone microenvironment (BM) is a complex ecosystem of cells (osteoclast, osteoblast, etc) & bone matrix
- In early breast cancer, the BM is: 1) premetastatic niche; 2) tumor sanctuary; 3) incubator for drug resistance
- Tumor hijacks the BM in the vicious cycle: tumor secretes cytokines → osteoblast drives osteoclast (OC) → release growth factors.
- Zoledronic acid (ZA) incorporated into bone; OC poisoned when ingests bone. Denosumab blocks OC growth factor.
- Menopause increases bone turnover releasing growth factors that support tumor growth
- Cochrane analysis of clinical trials shows no benefit for adjuvant anti-osteoclast therapy. Not standard of care.
- New hypotheses: estrogen rich BM → ZA resistance;
- SWOG 0307, D-CARE, ABCSG-18
Mechanisms of Tumor Associated Osteolysis in Solid Tumors

Coleman R. J Natl Cancer Inst 2012; 104:1059

Adjuvant Bisphosphonates to Reduce Recurrence Ibandronate Trial

- 1 randomized trial of 2 years ibandronate (50 mg po daily) in early stage breast cancer patients receiving anthracycline/taxane chemo (GAIN Trial)
  - No disease free or overall survival benefit

Mobus V, et al. SABCS 2011. Abstract S2-4
Adjuvant Bisphosphonates to Reduce Recurrence
Zoledronic Acid Trials

• ABCSG-12
  – Premenopausal, ER+ pts receiving OS/endocrine therapy
  – Improved DFS and OS for q6 monthly zoledronic acid vs none

• ZO-FAST (and combined Z-FAST/ZO-FAST analysis)
  – Postmenopausal, ER+ pts receiving letrozole
  – Fewer recurrences for upfront q6 monthly zoledronic acid vs delayed (small numbers)

• AZURE
  – Early stage breast cancer receiving systemic therapy
  – No difference in DFS/OS for “intensive” adjuvant zoledronic acid
  – Postmenopausal subset benefit?