City Wide Medical Oncology Rounds
Friday Sept. 21st, 2007

The Latest is the Greatest…

Future Directions in the Management of Patients with Bone Metastases from Breast Cancer

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Princess Margaret Hospital
Campbell Family Institute for Breast Cancer Research
Conflict of interest

• Clinical Research Protocols
  – Roche (ibandronate)

• Lab studies
  – Amgen (denosumab), Novartis (zoledronic acid)

• Talks
  – AstraZeneca (zactima), Novartis (zoledronic acid), Roche (ibandronate)

• Bone Metastases Program at PMH
  – Novartis (zoledronic acid)
Treating bone metastases

How does bone, “health” affect my patients?

Preserving bone mineral density
Preventing metastases
Background

• Metastatic breast cancer
• Bone metastases
  – incidence
  – consequences
• Why does breast cancer go to bone?
• Are current management strategies the, “best”?
• Clinical Trials
• The Future
## Metastatic Bone Disease is Common

<table>
<thead>
<tr>
<th>Tumor</th>
<th>5-year world prevalence, thousands(^1)</th>
<th>Incidence of BM in cancers(^2)</th>
<th>Median survival, Months(^2-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma</td>
<td>144</td>
<td>70 - 95</td>
<td>6 - 54</td>
</tr>
<tr>
<td>Renal</td>
<td>480</td>
<td>20 - 25</td>
<td>12</td>
</tr>
<tr>
<td>Melanoma</td>
<td>533</td>
<td>14 - 45</td>
<td>6</td>
</tr>
<tr>
<td>Bladder</td>
<td>1,000</td>
<td>40</td>
<td>6 - 9</td>
</tr>
<tr>
<td>Thyroid</td>
<td>475</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td>Lung</td>
<td>1,394</td>
<td>30 - 40</td>
<td>6 - 7</td>
</tr>
<tr>
<td><strong>Breast</strong></td>
<td><strong>3,860</strong></td>
<td><strong>65 - 75</strong></td>
<td><strong>19 - 25</strong></td>
</tr>
<tr>
<td>Prostate</td>
<td>1,555</td>
<td>65 - 75</td>
<td>12 - 53</td>
</tr>
</tbody>
</table>

Bone metastases are common and important!

- Over 5,000 Canadian women will die of breast cancer this year

- Majority either presented with or subsequently developed bone metastases (BM)

- Two-thirds of patients with BM will subsequently develop skeletal related events (SRE)
What do I do for Mrs J?

- Confirm that she has metastatic breast cancer
- Tell her it is incurable
- Consider radiotherapy for pain in back (or US trial)
- Change tamoxifen (or trial)
- Start a bisphosphonate (or trial)
What do I do for Mrs J?

- She then says,

“What does the future hold for me with all these bone metastases?”
Consequences of bone metastases in breast cancer: Mortality

- Median overall survival of patients with
  - bone only or dominant disease: 2–3 years
  - pathologic fracture: 12 months
  - spinal cord compression: 4 months
  - hypercalcemia: 3 months
The Bisphosphonates

• Inhibitors of osteoclast-mediated bone resorption

• BPs plus to chemo or hormonal therapy significantly
  – Reduce and delay SREs

• An integral part of clinical practice of patients newly diagnosed with BM
The bisphosphonates are not a panacea!

- Still need analgesia, surgery, radiotherapy, chemo / endocrine therapy
- Even with IV BP around 50% will not have a symptomatic response
- Absolute reduction in number and rate of SREs 13%
- Even with the most “potent” BP zoledronic acid therapy 30% of patients will have SREs in the following 2 years
- Maximisation of BP benefit is needed either:
  - Some patients do not need a BP
  - BPs are ineffective in some patients
  - Route and schedule of administration are not optimal
Can we use bisphosphonates more effectively i.e. why is the absolute benefit so small?

• **When should we START bisphosphonates?**
  - practice guidelines: initiate BPs at diagnosis of bone metastases

• **Breast cancer trials contain highly selected patients i.e. the one size fits all model does not work!**
  - majority bone-only disease (61–70%)
  - overall 13% reduction in SREs: population with a relatively favorable prognosis
  - eligibility criteria include a prognosis of >6 months survival
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Bone only disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>S&amp;W</td>
<td>190</td>
<td>29%</td>
</tr>
<tr>
<td>Hortobagyi 1996</td>
<td>380</td>
<td>60-62%</td>
</tr>
<tr>
<td>Theriault 1999</td>
<td>372</td>
<td>66-72%</td>
</tr>
<tr>
<td>Body 2003</td>
<td>466</td>
<td>65-68%</td>
</tr>
<tr>
<td>Tripathy 2004</td>
<td>435</td>
<td>NA</td>
</tr>
<tr>
<td>Kohno 2005</td>
<td>228</td>
<td>49%</td>
</tr>
</tbody>
</table>
Percentage of patients with bone only disease

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Bone only disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>James</td>
<td>267</td>
<td>32%</td>
</tr>
<tr>
<td>Plunkett</td>
<td>859</td>
<td>25-35%</td>
</tr>
</tbody>
</table>

The incidence of fractures
- highest in pts with bone only metastases
- lowest in those with co-existing liver disease.


There are essentially 3 groups of patients:

**Lower risk group**
- where SREs are not a great issue

**High risk group**
- who with appropriate therapy can move to the (and hopefully stay there)

**Worst risk group**
- whatever you do they will continue to have SREs, need new treatment strategies

- Probably over treated
- Correctly treated
- Need to be better treated
Increased Bone Resorption is the Hallmark of Metastatic Bone Disease

NTX excretion (nmol/mm mol creatinine)

- **Pathological >100**
- **Postmenopausal women /older men 50-100**
- **Normal young women/men 0-50**

Prostate (n=611)  | Breast (n=744)  | Myeloma (n=318)

Coleman et al - J Clin Oncol 2005
Can N-telopeptide be used to guide more effective treatment strategies for patients with bone metastases?

- NTX is correlated with:
  - Presence of bone mets
  - Symptoms
  - Response to treatment
  - Progression
  - Survival
Use of Bone Resorption Markers to Direct Zoledronic Acid Therapy - BISMARK

- 1400 patients with bone metastases from breast cancer
- Bone resorption assessed every 16 weeks- Urinary NTX
- Primary endpoint: Risk of skeletal events (SRE) with time
- Non-inferiority design

Bone marker (NTX) directed therapy Q 4, 8 or 16 weeks
Zoledronic acid 4mg iv 3-4 weekly
Zoledronic Acid

Worst Pain Score

Box & Whisker Plot: Worst Pain Score

Baseline Week 1 Week 2 Week 3 Week 4 Week 8

±1.96*Std. Err. ±1.00*Std. Err. Mean

±95%CI

Baseline Week 1 Week 2 Week 3 Week 4 Week 8

*p = 0.081 and 0.028

Oral Ibandronate

Worst Pain Score

Box & Whisker Plot: Worst Pain Score

Baseline Week 1 Week 2 Week 3 Week 4 Week 8 Week 12

±1.96*Std. Err. ±1.00*Std. Err. Mean

±95%CI

Baseline Wk 1 Wk 2 Wk 3 Wk 4 Wk 8 Wk 12

*p = 0.008 and 0.028

Number of Pain Sites

Box & Whisker Plot: Number of Pain Sites Reported

Baseline Week 1 Week 2 Week 3 Week 4 Week 8 Week 12

±1.96*Std. Err. ±1.00*Std. Err. Mean

±95%CI

Baseline Wk 1 Wk 2 Wk 3 Wk 4 Wk 8 Wk 12

*p = 0.037 and 0.004

Urinary NTX Levels

Box & Whisker Plot: Log NTX (corrected for Cr) Over Time

Baseline Week 1 Week 2 Week 3 Week 4 Week 8 Week 12

±1.96*Std. Err. ±1.00*Std. Err. Mean

±95%CI

Baseline Wk 1 Wk 2 Wk 3 Wk 4 Wk 8 Wk 12

*p = 0.008

*p < 0.01

*p < 0.01
Bone Biopsy Program
RANK/RANKL Pathway
Mechanism of action of AMG 162 – RANKL is a critical mediator of OC differentiation, function and survival.
So what’s new?
AMG 162 (Denusomab)

- Fully human monoclonal antibody to RANKL
- Opposes osteoclast differentiation and activation by binding to RANK-Ligand
Breast Cancer Phase 1: Inhibition of Bone Turnover in AMG 162 vs. Pamidronate

A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects with Advanced Breast Cancer (20050136)

Status:
Recruiting

Purpose:
The purpose of this study is to determine if denosumab is non-inferior to zoledronic acid in the treatment of bone metastases in subjects with advanced breast cancer

Phase 3
Summary

• Bone is the most common site of recurrence of breast cancer

• Presence of bone metastases and the occurrence of skeletal related events affects both morbidity and mortality

• Despite the widespread use of BPs it remains unclear
  – Magnitude of individual benefit?
  – Which BP to use?
  – Who to treat?
  – When to treat?
  – For how long?

• Biomarkers of bone destruction now exist and will hopefully enable improved targeting of patients in the future
So...

Is The Latest the Greatest?

Future Directions in the Management of Patients with Bone Metastases from Breast Cancer
Fixed Schedule Treatment

NTX level

Bisphosphonate treatments

Durable endocrine response
? Over-treated

SRE

Aromatase Inhibitor

Rob Coleman

Weeks

26 treatments
Over 112 weeks

1 SRE
Marker Directed Treatment

Sequential response and progression

Bisphosphonate treatments

15 treatments Over 112 weeks
3 SRE

NTX level

Non-steroidal Al
Exemestane
Docetaxel

Rob Coleman
So...

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These agents are not without side effects – that may become increasingly important if bisphosphonates move into the adjuvant setting