Bone targeting: bisphosphonates, RANK-ligands and radioisotopes

Dr Lisa Pickering
Consultant Medical Oncologist
ESMO Preceptorship Singapore 2017
## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Entities</th>
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<tbody>
<tr>
<td>Institutional Research Support/P.I.</td>
<td>Novartis, Pfizer, Pierre Fabre</td>
</tr>
<tr>
<td>Employee</td>
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<tr>
<td>Consultant</td>
<td>Astellas, BMS, EUSA Pharma, Ipsen, Janssen, MSD, Novartis, Pfizer</td>
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<tr>
<td>Major Stockholder</td>
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<td>Speakers Bureau</td>
<td>BMS, EUSA Pharma, Novartis, Pfizer</td>
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<td>Honoraria</td>
<td>Astellas, Ipsen, Janssen, MSD, Pfizer</td>
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<tr>
<td>Scientific Advisory Board</td>
<td>Astellas, EUSA Pharma, Ipsen, Janssen, MSD, Novartis, Pfizer, Sanofi</td>
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Why target bone in prostate cancer?

- Treat established bone metastases:
  - Bone-related progression
  - Bone-related symptoms

- Reduce risk of developing bone metastases?

- Improve survival?
CRPC pattern of disease over time

- The skeleton is the most common site of metastasis in prostate cancer\(^1\)
- 90% of men with metastatic prostate cancer have bone metastases\(^2\)

Bone metastases are associated with significant morbidity:

**Skeletal-related events (SREs)**

- Pain, Fracture
- Spinal cord compression
- Radiation or surgery to bone
- Hypercalcemia

**Morbidity**: decreased emotional & physical QoL\(^1, 2\)

**Cost**: higher healthcare costs for patients with SREs\(^3, 4\)

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Bone Lesions, %</th>
<th>SREs(^5, 6), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>65-75</td>
<td>68</td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
<td><strong>90(^6)</strong></td>
<td><strong>49</strong></td>
</tr>
<tr>
<td>Lung</td>
<td>30-40</td>
<td>48</td>
</tr>
<tr>
<td>Myeloma</td>
<td>95-100</td>
<td>51</td>
</tr>
</tbody>
</table>

When targeting bone, need to consider bone biology:
Bone remodeling: a reminder…

Bone Formation
- Osteoblasts express osteoclastogenic factors
- Stimulation of osteoblast differentiation
- Release of osteoinductive factors

Bone Resorption
- Stimulation of osteoclast formation
- Osteoblasts express osteoclastogenic factors

Diagram:
- Bone Formation
- Bone Resorption
- Stimulation of osteoblast differentiation
- Release of osteoinductive factors
- Osteoblasts express osteoclastogenic factors
- Stimulation of osteoclast formation
Prostate cancer and bone interaction: A vicious cycle with “uncoupling” of usual bone biology

Prostate cancer cells

Bone-derived growth factors

Osteoblasts

Mineralized bone matrix

Osteoclasts

Osteoelastic factors

New bone


Greg Mundy, Nat Rev Cancer 2002
To add a few specifics…
The pathophysiology of cancer-related bone metastases in CaP

Osteoblastic\textsuperscript{[1]}
- Tumour production of osteoblast growth factors: PDGF, IGF, \& bone morphogenic proteins: adrenomedullin \& endothelin-1
- New bone formations leads to the release of growth factor: IL-6

Osteolytic\textsuperscript{[2]}
- Tumour secretion of factors that stimulate osteolysis: PTHrP, RANKL, IL-11, IL-8, \& IL-6
- Osteolytic release of growth factors stored in the bone matrix that stimulate tumor cells (eg, TGF-\(\beta\))

\textit{In prostate cancer, both mechanisms are involved}

Management strategies for metastatic bone disease

- Treat underlying disease. This can be very important, eg efficacy of first line ADT
  - Hormonal therapy
  - Systemic chemotherapy
  - External beam radiation

- Bone-directed therapy
  - Bisphosphonates (prevent bone resorption)
  - RANKL inhibitor (prevent bone resorption)
  - Bone-targeting radionuclides

Management strategies in relation to pathophysiology

• Bisphosphonates eg zoledronic acid
  – Induce osteoclast apoptosis
  – Inhibit osteoclast maturation, migration and function
  – Directly induce cancer cell apoptosis (importance?)

• RANK-L inhibitors eg denosumab
  – Humanised monoclonal antibody to RANK-ligand
  – RANK-ligand pivotal for osteoblast:osteoclast interaction
  – Therefore inhibits osteoclast activity
Zoledronic Acid in CRPC

Eligibility
- Castration resistant prostate cancer
- Bone metastases (>3 on bone scan) (N = 643)

- Patients in 8-mg arm reduced to 4 mg due to renal toxicity
- **Primary outcome**: proportion of patients having ≥ 1 SRE (included change in anti-neoplastic therapy to treat bone pain)
- Secondary outcomes: time to first on-study SRE, proportion of patients with SREs, and time to disease progression

Zoledronic Acid in CRPC: Time to First SRE

Zoledronic Acid in CRPC: Time to First SRE

- SREs: ZOL 4 mg 38%; Placebo 49% (p= .028)
  - 11% absolute risk reduction in ≥ 1 SRE
- Pain/analgesia scores increased less with ZOL
- No improvement in tumour progression, QoL, OS

Pain scores better with zoledronic acid than placebo

No difference in overall survival from with zoledronic acid compared with placebo.

RANKL inhibition: Mechanism of action

- Tumour cells
  - Increase expression of RANKL
  - Decrease expression of OPG
  - Increase bone resorption through osteoclast activity

Denosumab in prostate cancer: Phase III, non inferiority, RCT

Eligibility
• CRPC
• Bone metastases (N = 1901)

- All patients received supplemental calcium and vitamin D
- Primary endpoint: time to first on-study SRE
- Secondary endpoints: OS, time to progression,

Denosumab 120 mg SC + Placebo IV q4w (n = 950)

Zoledronic acid 4 mg IV + Placebo SC q4w (n = 951)

Denosumab vs Zol Acid: Time to first SRE

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Denosumab</th>
<th>Zoledronic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>950</td>
<td>951</td>
</tr>
<tr>
<td>3</td>
<td>758</td>
<td>733</td>
</tr>
<tr>
<td>6</td>
<td>582</td>
<td>544</td>
</tr>
<tr>
<td>9</td>
<td>472</td>
<td>407</td>
</tr>
<tr>
<td>12</td>
<td>361</td>
<td>299</td>
</tr>
<tr>
<td>15</td>
<td>259</td>
<td>207</td>
</tr>
<tr>
<td>18</td>
<td>168</td>
<td>140</td>
</tr>
<tr>
<td>21</td>
<td>115</td>
<td>93</td>
</tr>
<tr>
<td>24</td>
<td>70</td>
<td>64</td>
</tr>
<tr>
<td>27</td>
<td>39</td>
<td>47</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Denosumab</th>
<th>20.7 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZOL Acid</td>
<td>17.1 mos</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.82 (0.71-0.95)</td>
</tr>
<tr>
<td>P Value</td>
<td>0.008</td>
</tr>
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### Denosumab vs Zol Acid: Time to first SRE

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<th>ZOL Acid</th>
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<th>P Value</th>
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<tr>
<td>Median time to 1st SRE</td>
<td>20.7 mos</td>
<td>17.1 mos</td>
<td>0.82 (0.71-0.95)</td>
<td>0.008</td>
</tr>
<tr>
<td>OS</td>
<td>19.4</td>
<td>19.8</td>
<td>1.03 (0.91-1.17)</td>
<td>0.65</td>
</tr>
<tr>
<td>TTP</td>
<td>8.4</td>
<td>8.4</td>
<td>1.06 (0.95-1.18)</td>
<td>0.30</td>
</tr>
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</table>

Time to first & subsequent on-study SREs* (Multiple Event Analysis)

Rate ratio: 0.82 (95% CI: 0.71-0.94; $P = .008$)

Cumulative Mean Number of SREs per Patient

Events, n
- Denosumab: 494
- Zoledronic acid: 584

*Events occurring at least 21 days apart.

### Denosumab vs zoledronic acid: Significant adverse events

<table>
<thead>
<tr>
<th>Subject Incidence, n (%)</th>
<th>Zoledronic Acid (n = 945)</th>
<th>Denosumab (n = 943)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious serious adverse events</td>
<td>108 (11.4)</td>
<td>130 (13.8)</td>
</tr>
<tr>
<td>Acute-phase reactions (first 3 days)</td>
<td>168 (17.8)</td>
<td>79 (8.4)</td>
</tr>
<tr>
<td>Renal adverse events*</td>
<td>153 (16.2)</td>
<td>139 (14.7)</td>
</tr>
<tr>
<td>Cumulative rate of Osteonecrosis Jaw-ONJ</td>
<td>12 (1.3)</td>
<td>22 (2.3)</td>
</tr>
<tr>
<td>- Year 1</td>
<td>5 (0.5)</td>
<td>10 (1.1)</td>
</tr>
<tr>
<td>- Year 2</td>
<td>8 (0.8)</td>
<td>22 (2.3)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>55 (5.8)</td>
<td>121 (12.8)</td>
</tr>
</tbody>
</table>

- ONJ: Attention to dentition, duration & frequency of therapy
- Hypocalcaemia: monitor Ca, Mg, use supplementation
- Renal impairment
- Infusion reactions with zoledronic acid

Radiopharmaceutical therapies for targeting bone metastases

- Three agents approved:
  - Strontium-89: pure $\beta$ particle emitter
  - Samarium-153 EDTMP: $\beta$ and $\gamma$ particle emitter
  - Radium-223: $\alpha$ particle emitter

- $\beta$ particle emitters historically used for bone pain palliation but have limitations:
  - Haematologic toxicity
  - No effect on survival outcomes, PFS or OS
RESULTS OF A RANDOMIZED PHASE-III TRIAL TO EVALUATE THE EFFICACY OF STRONTIUM-89 ADJUVANT TO LOCAL FIELD EXTERNAL BEAM IRRADIATION IN THE MANAGEMENT OF ENDOCRINE RESISTANT METASTATIC PROSTATE CANCER

A. T. PORTER, M.D.,1 A. J. B. MCEWAN, M.D.,2 J. E. POWE, M.D.,3 R. REID, M.D.,3
D. G. McGOWAN, M.D.,2 H. LUKKA, M.D.,4 J. R. SATHYANARAYANA, M.D.,4
V. N. YAKEMCHUK, M.D.,4 G. M. THOMAS, M.D.,5 L. E. ERLICH,5 J. CROOK, M.D.,6
K. Y. GULENCHYN, M.D.,6 K. E. HONG, M.D.,7 C. WESOLOWSKI, M.D.7
AND J. YARDLEY, PH.D.8

Samarium-153 EDTMP vs Placebo: Efficacy in palliation

An alpha-emitter should be more active

<table>
<thead>
<tr>
<th></th>
<th>(\alpha) eg radium</th>
<th>(\beta) eg strontium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative mass</td>
<td>7300</td>
<td>1</td>
</tr>
<tr>
<td>Range in tissue</td>
<td>0.1mm</td>
<td>5mm</td>
</tr>
<tr>
<td>Hits to kill a cell</td>
<td>1–10</td>
<td>100–1000</td>
</tr>
</tbody>
</table>

\(\text{LET, linear energy transfer}\)

An alpha-emitter should be less toxic
Radium is chemically similar to calcium

So readily binds to bone
ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design

- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases

Randomised

Radium-223 (50 kBq/kg)
4 weekly, x6
+ Best standard of care

Placebo (saline)
+ Best standard of care

N = 922

Clinicaltrials.gov identifier: NCT00699751.

Parker et al. NEJM (2013)
ALSYMPCA: Overall survival improvement with radium vs placebo

Hazard ratio, 0.70 (95% CI, 0.58–0.83)  
P<0.001

Radium-223  
(median overall survival, 14.9 mo)

Placebo  
(median overall survival, 11.3 mo)

No. at Risk
Radium-223  
614 578 504 369 274 178 105 60 41 18 7 1 0 0
Placebo  
307 288 228 157 103 67 39 24 14 7 4 2 1 0

Parker et al. NEJM (2013)
ALSYMPCA: Time to first SRE improved with radium v placebo

**B Time to First Skeletal Event**

Hazard ratio, 0.66 (95% CI, 0.52–0.83)  
P<0.001

- Radium-223 (median overall survival, 15.6 mo)
- Placebo (median overall survival, 9.8 mo)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Radium-223</th>
<th>Placebo</th>
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<tr>
<td>614</td>
<td>496</td>
<td>342</td>
</tr>
<tr>
<td>307</td>
<td>211</td>
<td>117</td>
</tr>
</tbody>
</table>

*Parker et al. NEJM (2013)*
ALSYMPCA: Pain score better with radium-223

ALSYMPCA: Waterfall plot of maximum decline in ALP up to week 12

A. Placebo Arm  n = 211

B. Ra-223 Arm n = 497

ALSYMPCA: Radium is well-tolerated with no excess overall or haem AEs

How to make best use of radium-223: Issues for practical use

• Patient selection
  – Consider in all patients with bony metastatic CRPC

• Can be combined with other CaP treatments
  – Use with best available AR targeted therapy
  – Select patients with response to the first course and no problematic toxicity can be re-treated later

• Monitoring response
  – PSA does not necessarily tell the story
  – DW-MRI appears promising
Suggested mCRPC treatment paradigm for patients with bone-dominant metastases

1. LHRHa + Abiraterone
2. Add **radium-223** on PSA progression
3. Docetaxel
4. Cabazitaxel
Markers of bone resorption

• Includes eg urinary NTX and CTX
• Suppressed by zoledronic acid and denosumab
• Suppressed for many months after a single dose

• Is this useful in practice? – No routine use
Bone metastases in CaP: Conclusions

• Bone metastases affect 90% of pts with metastatic CaP & are associated with major morbidity & cost.

• Bone directed therapy limits the consequence of bone metastases (ie SREs) in CRPC.
  – No proven role in non metastatic CaP or in CSPC.

• Denosumab superior to ZA for SREs overall. Neither improves survival endpoints.

• Radium delays SREs with minimal toxicity and improves survival outcomes and can be given with other life-prolonging hormone therapies.
Thank you