Bone complications and management

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Bone is the most prevalent site of metastasis in castration-resistant prostate cancer patients.

Epidemiological data from docetaxel trials

Bone metastases can result in serious and debilitating SREs

- SREs are defined as:¹

<table>
<thead>
<tr>
<th>Pathological fracture</th>
<th>Radiation to bone</th>
<th>Surgery to bone</th>
<th>Spinal cord compression</th>
</tr>
</thead>
<tbody>
<tr>
<td>29%</td>
<td>22%</td>
<td>7%</td>
<td>3%</td>
</tr>
</tbody>
</table>

- Incidence in metastatic prostate cancer:²*
- Prior SRE increases the risk of subsequent SREs³
- Note that SRE frequencies depend on detection methods

²Proportion of patients with metastatic CRPC who experienced SRE(s) in the placebo arm of a 15-month study

¹
²
³


*Proportion of patients with metastatic CRPC who experienced SRE(s) in the placebo arm of a 15-month study
SRE frequency in trial of Ra-223 vs placebo

Radium-223 chloride (Alpharadin) impact on overall survival and skeletal-related events in patients with castration-resistant prostate cancer with bone metastases: A phase III randomized trial (ALSYMPCA). Sartor et al AUA 2012
The role of bone-targeting agents in metastatic CRPC

1. Radionuclides
2. Prevention of SREs
3. Prevention of metastases
The role of bone-targeting agents in metastatic CRPC

1. Radionuclides
2. Prevention of SREs
3. Prevention of metastases
Radionuclide/metabolic radiotherapy

Bone-seeking injectable radiopharmaceuticals
Indicated for multiple painful metastases
Main side effects: transient increase of pain, thrombopenia

<table>
<thead>
<tr>
<th>Radiopharmaceuticals</th>
<th>T/2</th>
<th>Track length</th>
<th>Emission</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{89}$Sr chloride</td>
<td>50.5 d</td>
<td>2.4 mm</td>
<td>$\beta$</td>
</tr>
<tr>
<td>$^{153}$Sm-EDTMP</td>
<td>1.93 d</td>
<td>0.6 mm</td>
<td>$\beta$</td>
</tr>
<tr>
<td>$^{186}$Re-HEDP</td>
<td>3.7 d</td>
<td>1.1 mm</td>
<td>$\beta$</td>
</tr>
<tr>
<td>$^{223}$Ra</td>
<td>11.4 d</td>
<td>0.1 mm</td>
<td>$\alpha$</td>
</tr>
</tbody>
</table>
**Strontium-89 vs External Beam RT in Prostate Ca**

Quilty et al 1994 Radioth. Oncol 31;33

- 284 pts with painful bone metastases.
- 3 way randomisation: 200 MBq Strontium-89
  - 20gy in 5 F local external beam RT
  - 6Gy x1 hemi-body external beam RT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Freedom from new painful metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 MBq Strontium-89</td>
<td>65%</td>
</tr>
<tr>
<td>20gy in 5 F local external beam RT</td>
<td>68%</td>
</tr>
<tr>
<td>6Gy x1 hemi-body external beam RT</td>
<td>67%</td>
</tr>
</tbody>
</table>

- At 12 weeks freedom from new painful metastases was 63.9% for SR-89 \( p < 0.05 \) vs 41.7% after local RT and 51.1% after hemi-body
- No significant OS difference
Summary
For Strontium and Samarium, there can be good relief of pain for several months, but there is no evidence of a survival benefit. There is mild bone marrow toxicity.
Radium-223: a new treatment for bone metastases

Experiments in mice suggested a marrow-sparing advantage for Radium-226.
Henriksen et al 2003

- High linear energy transfer enables DNA double strand breaks even in quiescent cells
- Short particle range limits toxicity to bone marrow
Placebo-Controlled Phase II Study of Radium-223 in Castration-Resistant Prostate Cancer

HR = 0.48; \( P = 0.017 \)
Median OS 65 vs 46 weeks

Radium-223, n = 33  4x 50mBq/kg
Placebo, n = 31

<table>
<thead>
<tr>
<th></th>
<th>Radium-223</th>
<th>Placebo</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>-24%</td>
<td>+45%</td>
<td>0.003</td>
</tr>
<tr>
<td>PINP</td>
<td>-63%</td>
<td>+38%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Radium-223</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>155</td>
<td>174</td>
</tr>
</tbody>
</table>

**ALSYMPCA: Study Design**

- **n=921** symptomatic mCRPC
  - ≥ 2 bone metastases
  - No known visceral metastases
  - Post-docetaxel or unfit for docetaxel

**Efficacy end points**
- Primary end point: OS
- Secondary end points: TTPP, TTP in total-ALP, safety, HRQoL

2:1

- **Six injections**
  - Radium-223 chloride
  - 50 kBq/kg IV every 4 weeks
  - (n=614)
  - Best supportive care

- **Six injections placebo**
  - every 4 weeks
  - (n=307)
  - Best supportive care

Planned follow-up is 3 years

ALSYMPCA: Overall Survival

Hazard ratio, 0.70 (95% CI, 0.58–0.83)
P<0.001
30% reduction in risk of death

ALSYMPCA: Symptomatic Skeletal-Related Events

## ALSYMPCA: Adverse Events of Interest

<table>
<thead>
<tr>
<th>Hematologic</th>
<th>All Grades</th>
<th>Grades 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radium-223 (n=600) n (%)</td>
<td>Radium-223 (n=600) n (%)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=301) n (%)</td>
<td>Placebo (n=301) n (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>187 (31)</td>
<td>76 (13)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (5)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69 (12)</td>
<td>38 (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>300 (50)</td>
<td>125 (21)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (25)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>213 (36)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111 (18)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>108 (18)</td>
<td>6 (1)</td>
</tr>
</tbody>
</table>

### ALSYMPCA: Survival benefit across patient subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>N</th>
<th>Hazard ratio</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td>809</td>
<td></td>
<td>0.695</td>
<td>0.552-0.875</td>
</tr>
<tr>
<td>Total ALP</td>
<td>&lt;220 U/L</td>
<td>452</td>
<td></td>
<td>0.691</td>
<td>0.497-0.962</td>
</tr>
<tr>
<td></td>
<td>≥220 U/L</td>
<td>357</td>
<td></td>
<td>0.689</td>
<td>0.504-0.941</td>
</tr>
<tr>
<td>Current use of bisphosphonates</td>
<td>Yes</td>
<td>331</td>
<td></td>
<td>0.582</td>
<td>0.397-0.854</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>478</td>
<td></td>
<td>0.752</td>
<td>0.567-0.999</td>
</tr>
<tr>
<td>Prior use of docetaxel</td>
<td>Yes</td>
<td>470</td>
<td></td>
<td>0.755</td>
<td>0.565-1.009</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>339</td>
<td></td>
<td>0.611</td>
<td>0.423-0.883</td>
</tr>
<tr>
<td>Baseline ECOG status</td>
<td>0 or 1</td>
<td>696</td>
<td></td>
<td>0.691</td>
<td>0.535-0.892</td>
</tr>
<tr>
<td></td>
<td>2 or higher</td>
<td>110</td>
<td></td>
<td>0.731</td>
<td>0.398-1.343</td>
</tr>
</tbody>
</table>

How do you monitor response to Ra-223?

Baseline
PSA 316
Alk Phos 1921

After Ra-223
PSA 204
Alk Phos 680
Guidelines on Prostate Cancer

Ra 223 improves survival in men with bone predominant disease without visceral metastasis. 1b A

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External Beam Radiotherapy in Metastatic Prostate Cancer

1. Relief of pain from bone metastasis
2. Relief of spinal cord compression
Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8-Gy arm (n = 288)</td>
</tr>
<tr>
<td>BPI worst pain score</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>44 (15)</td>
</tr>
<tr>
<td>1–4</td>
<td>99 (34)</td>
</tr>
<tr>
<td>5–6</td>
<td>56 (19)</td>
</tr>
<tr>
<td>7–10</td>
<td>89 (31)</td>
</tr>
<tr>
<td>No answers/2 answers</td>
<td>2</td>
</tr>
<tr>
<td>Overall response type</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>44 (15)</td>
</tr>
<tr>
<td>Partial</td>
<td>143 (50)</td>
</tr>
<tr>
<td>Stable</td>
<td>74 (26)</td>
</tr>
<tr>
<td>Progressive</td>
<td>27 (9)</td>
</tr>
</tbody>
</table>

Prevention of Spinal Cord Compression

• Spinal Cord Compression (SCC) is the most significant complication due to spinal skeletal metastasis.

• 3 – 10% of cancer patients resulting in significant debility and impact on quality of life.

• Clinical signs are unreliable indicators of the presence of the level of suspected SCC.

• MRI considered to be a mandatory investigation for detecting SCC and for planning management.

• In prostate cancer – investigations have shown it is possible to detect early radiological signs of impending SCC in asymptomatic patients with or without bone pain.
A Prospective Randomised Phase III Study of Observation Versus Screening MRI And Pre-Emptive Treatment in Castrate Resistant Prostate Cancer Patients With Spinal Metastasis

Eligible patient group:
CRPC patients with spinal metastasis.
No bony back pain.
No neurologic deficit.
No previous SCC (SCC).
Able to have MRI scan.

RANDOMISE

Control Group

Intervention Group

Pre-emptive treatment if radiological SCC on screening MRI spine.
Further 6 monthly screening MRI spine

Launched 2013 Total n=541. CI David Dearnaley (RMH & ICR). ICR Trials Unit. Sponsor: Cancer Research UK
In the management of painful bone metastases, early use of palliative treatments such as radionuclides, external beam radiotherapy and adequate use of analgesics is recommended.

<table>
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<tr>
<th></th>
<th>1a</th>
<th>B</th>
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</table>

In patients with neurological symptoms, spinal surgery or decompressive radiotherapy might be indicated as emergency interventions. High-dose corticosteroids must be always initially considered.

<table>
<thead>
<tr>
<th></th>
<th>1b</th>
<th>A</th>
</tr>
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</table>
Conclusions

• Radiotherapy is a useful low toxicity treatment for bone pain in patients with metastases from prostate cancer
• Single fraction external beam treatments are as effective at pain relief as longer schedules
• Systemic bone-seeking isotopes in the past have shown both pain relief and a delay to the next skeletal event
• Radium-223 is a significant advance in isotope treatment, not only causing effective pain relief and delaying further pain, but also prolonging survival
Bone targeted Therapies in mCRPC

Zoledronic acid binds to hydroxyapatite preventing the activity of osteoclasts and stimulating osteoblasts

Denosumab binds to RANKL preventing its binding to RANK thus inhibiting osteoclasts

Radiopharmaceuticals emit α or β ionizing radiation to tumor cells in bone

El-Amm, Freeman, Patel, Aragon-Ching, Prostate Cancer 2013)
Interrupting the vicious cycle of bone metastases

ETaR inhibitors

ET\textsubscript{1} ...

Tumour cells

Denosumab

Bisphosphonates

Activated osteoclast

RANK Ligand

RANK

OPG

Bisphosphonates in the treatment of bone metastases from prostate cancer

<table>
<thead>
<tr>
<th>Test drug</th>
<th>N</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td>57</td>
<td>Transient pain reduction</td>
<td>Smith, 1989, J.Urol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo-controlled studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate</td>
<td>311</td>
<td>No significant benefit</td>
<td>Dearnaley, 2003, JNCI</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>378</td>
<td>No significant benefit</td>
<td>Small, 2003, JCO</td>
</tr>
<tr>
<td>Clodronate</td>
<td>209</td>
<td>No significant benefit</td>
<td>Ernst, 2003, JCO</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>643</td>
<td>Significant delay of SRE</td>
<td>Saad, 2002/2004, JNCI</td>
</tr>
</tbody>
</table>
At 2 years zoledronic acid reduced all SREs in PCa patients with bone metastases.

P = 0.028

SRE, skeletal-related event; PCa, prostate cancer; HCM, hypercalcemia of malignancy
Adapted from Saad F, et al. Poster presented at: 19th EAU Congress; March 24-27, 2004; Vienna, Austria. Poster 615.
Zoledronic acid resulted in better control of pain versus placebo over 2 years in patients with PCa

PCa, prostate cancer; BPI, Brief Pain Inventory.
*P < 0.05.
Saad et al. BJU Int. 2006;96:964-969.
Prostate cancer: zoledronic acid reduced the risk of SREs regardless of prior SRE history

Before study entry

<table>
<thead>
<tr>
<th></th>
<th>Risk reduction</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior SRE</td>
<td>33%</td>
<td>.027</td>
</tr>
<tr>
<td>Prior SRE</td>
<td>40%</td>
<td>.028</td>
</tr>
<tr>
<td>Overall trial population</td>
<td>36%</td>
<td>.002</td>
</tr>
</tbody>
</table>

SRE, skeletal-related event
SRE Free Interval: ZA comparison

Analysis
Univariable: HR 0.75 (0.61, 0.93); p=0.008

Median
13.1 (11.5, 16.4) mths

18.1 (14.2, 23.4) mths

Patients at risk
No ZA 381 275 140 66 36
ZA 376 299 164 79 38
Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

Key eligibility criteria
- CRPC
- Bone metastasis
- No prior IV bisphosphonates

Denosumab
120 mg SC Q4W
+ Placebo IV Q4W

Zoledronic acid
4 mg IV Q4W
+ Placebo SC Q4W

Primary objective: Efficacy (non-inferiority)
Secondary objectives: Efficacy (superiority), multiple SRE analysis, safety

Fizazi et al. Lancet 2011; 377: 813–22
Denosumab significantly delayed time to first on-study SRE compared with zoledronic acid.

- **Denosumab**: KM estimate of median (months) = 20.7
- **Zoledronic acid**: KM estimate of median (months) = 17.1

HR 0.82 (95% CI: 0.71, 0.95)

P = 0.0002 (Non-inferiority)
P = 0.008 (Superiority)

Fizazi et al. Lancet 2011; 377: 813–22
Denosumab significantly delayed time to first and subsequent on-study SREs* compared with zoledronic acid

*Events occurring at least 21 days apart (multiple event analysis)

Rate ratio = 0.82 (95% CI: 0.71, 0.94)
P = 0.008

Denosumab significantly delayed time to first and subsequent on-study SREs* compared with zoledronic acid

Fizazi et al. Lancet 2011; 377: 813–22
Overall survival was comparable between groups

HR=1.03 (95% CI, 0.91–1.17); P=0.65

No. at risk
Zoledronic acid 951 864 745 635 519 401 297 207 143 98 55
Denosumab 950 872 746 645 552 427 310 233 156 99 54

Fizazi et al. Lancet 2011; 377: 813–22
Adverse events were well balanced and as expected for this patient population

<table>
<thead>
<tr>
<th>Subject incidence, n (%)</th>
<th>Zoledronic acid (n=945)</th>
<th>Denosumab (n=943)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>918 (97)</td>
<td>916 (97)</td>
</tr>
<tr>
<td>Most common AEs in either arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>341 (36)</td>
<td>337 (36)</td>
</tr>
<tr>
<td>Back pain</td>
<td>287 (30)</td>
<td>304 (32)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>274 (29)</td>
<td>267 (28)</td>
</tr>
<tr>
<td>Nausea</td>
<td>245 (26)</td>
<td>272 (29)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>222 (24)</td>
<td>257 (27)</td>
</tr>
<tr>
<td>CTC Grade 3, 4, or 5 AEs</td>
<td>672 (71)</td>
<td>718 (76)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>568 (60)</td>
<td>594 (63)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation</td>
<td>138 (15)</td>
<td>164 (17)</td>
</tr>
</tbody>
</table>

Fizazi et al. Lancet 2011; 377: 813–22
AFFIRM: Time to first SRE

Fizazi et al. ESMO 2012; abstract 8960 (oral presentation)
Available at: http://www.esmo.org/events/esmo-congress-webcast-library.html
COU-AA-301: Time to SRE

SREs were documented in 22.6% of patients in the abiraterone + prednisone arm and 24.6% in the placebo + prednisone arm. Abiraterone + prednisone significantly delayed the time to SREs.

Guidelines on Prostate Cancer

Bone protective agents may be offered to patients with skeletal metastases (denosumab being superior to zoledronic acid) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided.

Calcium and vitamin D supplementation must be systematically considered when using either denosumab or biphosphonates.

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Conclusion

Bone metastases are central to prostate cancer
New generation of bone-seeking radionuclides offers new opportunities to control survival
Bone-targeted therapies help delay SREs and potentially metastases