Bone pain palliation therapy with β-emitters: $^{89}\text{Sr}$, $^{153}\text{Sm}$, $^{186/188}\text{Re}$

Francesco Cicone, MD

International course on theranostics and molecular radiotherapy
Brussels, 06-10-2017
The skeleton is commonly affected by metastatic disease (≈20%).

Breast and prostate cancer account for about 80% of all bone mets.
The clinical problem

- PAIN
- FRACTURES
- CORD COMPRESSION/INFILTRATION
- HIPERCALCEMIA

\[ \downarrow \]

- LIMITED MOBILITY
- REDUCTION SLEEP TIME

\[ \rightarrow \]

- WORSENING QUALITY OF LIFE
Therapeutic options

NSAIDs

Opioids

Bisphosphonates

Surgery (decompression/vertebroplasty/arthroplasty)

EBRT (localized and/or hemibody)

Deschamps & de Baere Diagnostic and Interventional Imaging 2012
Aboulafia AJ et al. Seminars in Oncology 2007
Simultaneous treatment of multiple sites. Greater chance to benefit: osteoblastic lesions, limited skeletal involvement.

Possibility of combination with other treatments modalities.

Reduction of analgesic drug consumption.

Reduction of new painful sites?

Radiopharmaceuticals for bone pain palliation: general characteristics

Kraeber-Bodere F et al. EJNM 2000

Quilty PM et al. Radiother Oncol 1994

Fig. 4. Freedom from newly arising sites of pain at each assessment visit, by study treatment.
Patient enrollment

1) Positive bone scan - single or multiple osteoblastic lesions

2) Matching between sites of pain and imaging

N.B. exclude vertebral collapses, fractures, visceral pain, spinal cord compression

Lewington V. JNM 2005; 46:38S-47S
Side effects/Toxicity

• Common pain “Flare” 24-48 h p.i. (steroids)
• Swelling, worsening of cord compression, potential risk of fracture (consider surgical stabilization before radionuclide therapy)
• Activity-dependent bone marrow toxicity
**Issues to consider**

Hematological stability (Hb > 9 mg/dL ; PLT >100,000/mm$^3$)

Higher likelihood of toxicity in «Superscans»

Adequate renal function

Consider activity reduction if GFR<50 mL/min

Not recommended if GFR<30 mL/min

Hemibody radiation >6 weeks before

Urinary obstruction should be checked for and solved before therapy
Retreatment

1st cycle $^{153}\text{Sm}$-EDTMP

3rd cycle $^{153}\text{Sm}$-EDTMP

$T=0$  $T=1\text{ y}$
Mechanism of action

Pain palliation does not directly depend on cell killing

Mechanical changes (decompression, tumor shrinkage) cannot explain the rapid onset of pain relief

Bone microenvironment: radiation-induced humoral changes (modification of cytokines), reduction of tissutal reaction
### Physical characteristics of available β- emitting radioisotopes

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>β Energy max (MeV)</th>
<th>Energy Mean (MeV)</th>
<th>Max Range (mm)</th>
<th>Gamma emission</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{89}$Sr</td>
<td>50.5 days</td>
<td>1.4</td>
<td>0.583</td>
<td>7 mm</td>
<td>NO</td>
</tr>
<tr>
<td>$^{186}$Re</td>
<td>89 hours</td>
<td>1.07</td>
<td>0.362</td>
<td>5 mm</td>
<td>137 keV</td>
</tr>
<tr>
<td>$^{153}$Sm</td>
<td>46.3 hours</td>
<td>0.81</td>
<td>0.229</td>
<td>4 mm</td>
<td>103 keV</td>
</tr>
<tr>
<td>$^{188}$Re</td>
<td>17 hours</td>
<td>2.1</td>
<td>0.764</td>
<td>10 mm</td>
<td>155 keV</td>
</tr>
</tbody>
</table>

Half-life  →  Dose-rate  →  **Onset/duration of pain relief**

β energy  →  particle range  →  **Toxicity/cell killing**

γ emission  →  γ camera imaging  →  **dosimetry**
**89 Strontium Chloride (Metastron®)**

![Diagram of the periodic table with Strontium highlighted]

For elements with no stable isotopes, the mass number of the isotope with the longest half-life is in parentheses.
$^{89}\text{SrCl}_2$

Recommended activity: 148 MBq (4 mCi)
Outpatient administration
No dose-efficacy correlation found (plateau at 1.5 MBq/Kg)

Delayed onset of pain relief (7-20 days)
Long duration of pain relief (4-6 months)

Imaging/dosimetry with $^{85}\text{Sr}$ (514 keV, 64 days half-life…not ideal!)
$^{153}$SAMARIUM-EDTMP (QUADRAMET®)

Recommended activity: 37 MBq/Kg (1 mCi/Kg)

Improved response (clinical/biochemical) with increasing activity

Early onset of pain relief (48-72 hours)

Short duration of pain relief (6-8 weeks)

Imaging/dosimetry feasible with gamma cameras
**186 RENIUM-HEDP (RE-BONE®)**

(abandoned)

Recommended activity: 1295 MBq (35 mCi)

Improved response with increasing activity

Early onset of pain relief (24-48 hours)

Short duration of pain relief (6-8 weeks)

Imaging/dosimetry feasible with gamma cameras

Quirijinen JMSp et al. JNM 1996
### Efficacy – Summary of available studies

<table>
<thead>
<tr>
<th>References</th>
<th>Year</th>
<th>No. of patients</th>
<th>Dose (SI)</th>
<th>Cancer Description</th>
<th>Pain Relief %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sr-89 chloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fuster et al</td>
<td>2000</td>
<td>40</td>
<td>4 mCi (148 MBq)</td>
<td>Breast Cancer</td>
<td>92%</td>
</tr>
<tr>
<td>Kraeger-Bodere et al</td>
<td>2000</td>
<td>94</td>
<td>4 mCi (150 MBq)</td>
<td>Prostate Cancer</td>
<td>78%</td>
</tr>
<tr>
<td>Turner et al</td>
<td>2001</td>
<td>93</td>
<td>4 mCi (150 MBq)</td>
<td>Prostate Cancer</td>
<td>63%</td>
</tr>
<tr>
<td>Dafermou et al</td>
<td>2001</td>
<td>527</td>
<td>4 mCi (149 MBq)</td>
<td>Prostate Cancer</td>
<td>59.90%</td>
</tr>
<tr>
<td>Ashayori et al</td>
<td>2002</td>
<td>27</td>
<td>4 mCi (150 MBq)</td>
<td>Prostate cancer and breast cancer</td>
<td>91%</td>
</tr>
<tr>
<td>Zorga et al</td>
<td>2003</td>
<td>33</td>
<td>4 mCi (149 MBq)</td>
<td>Prostate, breast, bladder, and renal cell cancer</td>
<td>92%</td>
</tr>
<tr>
<td>Baczyk et al</td>
<td>2003</td>
<td>70</td>
<td>4 mCi (148 MBq)</td>
<td>Prostate Cancer</td>
<td>88%</td>
</tr>
<tr>
<td>Gunawardana et al</td>
<td>2004</td>
<td>13</td>
<td>4 mCi (148 MBq)</td>
<td>Prostate Cancer</td>
<td>57%</td>
</tr>
<tr>
<td>Liepe et al</td>
<td>2007</td>
<td>15</td>
<td>4 mCi (148 MBq)</td>
<td>Prostate and breast cancer</td>
<td>72%</td>
</tr>
<tr>
<td>Ma et al</td>
<td>2008</td>
<td>116</td>
<td>40-60 uCi/kg (1.48-2.22 MBq/kg)</td>
<td>Prostate Cancer</td>
<td>83.90%</td>
</tr>
<tr>
<td>Sm-153 Ioxadron</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serafini et al</td>
<td>1998</td>
<td>118</td>
<td>0.5-1 mCi/kg (19.5-37 MBq/kg)</td>
<td>Prostate, breast, others cancer</td>
<td>62%-82%</td>
</tr>
<tr>
<td>Tian et al</td>
<td>1999</td>
<td>105</td>
<td>1 mCi/kg (37 MBq/kg)</td>
<td>Prostate, breast, others cancer</td>
<td>84%</td>
</tr>
<tr>
<td>Dolezal et al</td>
<td>2000</td>
<td>33</td>
<td>1 mCi/kg (37 MBq/kg)</td>
<td>Prostate, breast, others cancer</td>
<td>70%</td>
</tr>
<tr>
<td>Wang et al</td>
<td>2003</td>
<td>9</td>
<td>1 mCi/kg (37 MBq/kg)</td>
<td>Prostate, breast, others cancer</td>
<td>78%</td>
</tr>
<tr>
<td>Sapienza et al</td>
<td>2004</td>
<td>73</td>
<td>1 mCi/kg (37 MBq/kg)</td>
<td>Prostate breast cancer</td>
<td>76%</td>
</tr>
<tr>
<td>Etchebehere et al</td>
<td>2004</td>
<td>58</td>
<td>1.0-1.6 mCi/kg (37-59.2 MBq/kg)</td>
<td>Prostate, breast, others cancer</td>
<td>78%</td>
</tr>
<tr>
<td>Re-186 HEDP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sartor et al</td>
<td>2004</td>
<td>152</td>
<td>1 mCi/kg (37 MBq/kg)</td>
<td>Prostate Cancer</td>
<td>65%</td>
</tr>
<tr>
<td>Tripathi et al</td>
<td>2004</td>
<td>85</td>
<td>1 mCi/kg (37 MBq/kg)</td>
<td>Prostate, breast, others cancer</td>
<td>73%</td>
</tr>
<tr>
<td>Ripamonti et al</td>
<td>2007</td>
<td>13</td>
<td>1 mCi/kg (40 MBq/kg)</td>
<td>Prostate Cancer</td>
<td>61.50%</td>
</tr>
<tr>
<td>Liepe et al</td>
<td>2007</td>
<td>15</td>
<td>1 mCi/kg (37 MBq/kg)</td>
<td>Prostate and breast cancer</td>
<td>73%</td>
</tr>
<tr>
<td>Dolezal et al</td>
<td>2007</td>
<td>32</td>
<td>1 mCi/kg (37 MBq/kg)</td>
<td>Prostate Cancer</td>
<td>75%</td>
</tr>
<tr>
<td>Kolesnikov-Gauthier et al</td>
<td>2000</td>
<td>26</td>
<td>35 mCi (1295 MBq)</td>
<td>Prostate and breast cancer</td>
<td>50%</td>
</tr>
<tr>
<td>Tennyson et al</td>
<td>2000</td>
<td>14</td>
<td>70 mCi (2590 MBq)</td>
<td>Prostate Cancer</td>
<td>79%</td>
</tr>
<tr>
<td>Kucuk et al</td>
<td>2000</td>
<td>31</td>
<td>35 mCi (1295 MBq)</td>
<td>Prostate, breast, rectum, lung, and nasopharynx cancer</td>
<td>67.50%</td>
</tr>
<tr>
<td>Scifio et al</td>
<td>2000</td>
<td>60</td>
<td>38 mCi (1406 MBq)</td>
<td>Prostate and breast cancer</td>
<td>80%</td>
</tr>
<tr>
<td>Scifio et al</td>
<td>2000</td>
<td>20</td>
<td>38 mCi (1406 MBq)</td>
<td>Prostate Cancer</td>
<td>92%</td>
</tr>
<tr>
<td>Dafermou et al</td>
<td>2001</td>
<td>58</td>
<td>35 mCi (1295 MBq)</td>
<td>Prostate Cancer</td>
<td>88%</td>
</tr>
<tr>
<td>Han et al</td>
<td>2002</td>
<td>43</td>
<td>35 mCi (1295 MBq)</td>
<td>Prostate Cancer</td>
<td>65%</td>
</tr>
<tr>
<td>Leondi et al</td>
<td>2004</td>
<td>24</td>
<td>35 mCi (1295 MBq)</td>
<td>Lung Cancer</td>
<td>62%</td>
</tr>
<tr>
<td>Liepe et al</td>
<td>2007</td>
<td>15</td>
<td>35 mCi (1295 MBq)</td>
<td>Prostate and breast cancer</td>
<td>67%</td>
</tr>
</tbody>
</table>
## Dosimetry of available radiopharmaceuticals

<table>
<thead>
<tr>
<th>Organ</th>
<th>$^{89}\text{SrCl}_2$</th>
<th>$^{153}\text{Sm-EDTMP}$</th>
<th>$^{186}\text{Re-HEDP}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone surface</td>
<td>17</td>
<td>6.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Red marrow</td>
<td>11</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Lower Bowel wall</td>
<td>4.7</td>
<td>0.010</td>
<td>0.57</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.80</td>
<td>0.020</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Bodei L et al. EJNMMI 2008
How to choose (besides availability)?

Severity of pain
Life expectancy
Predicted toxicity

Who would you prefer to treat?

Pt 1

Pt 2
Does therapy with β-emitters prolong survival?

Registration trials had palliation only as primary endpoint.

Given the early approval, manufacturers did not have the need of running new trials with overall survival as primary endpoint.

There are trials suggesting a survival benefit for β emitters:

\[ {^{89}}\text{SrCl}_2 + \text{DOXO} \]

\[ \text{DOXO} \]

\[ \text{Tu SM et al. Lancet 2001; 357: 336–41} \]
Survival benefit of retreatment

Group A = single injection $^{188}\text{Re}$-HEDP
Group B = two injections $^{188}\text{Re}$-HEDP
Effects of $^{153}$Sm-EDTMP on circulating tumor cells

Scopinaro F et al. EANM Congress 2008
Conclusions

β-emitting radiopharmaceuticals are long standing efficacious weapons against bone pain. Benefits and adverse events can be optimized by careful patient selection. A survival advantage is likely although not specifically investigated. No comparison with newer α emitters exists.
Thanks for your attention