Clinical Use of Bone-Seeking Radiopharmaceuticals for Palliation of Metastatic Bone Pain

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Most Common Skeletal Metastasis

- Prostate (70%) ⇒ 80% osteoblastic
- Breast (70%) ⇒ 40% osteoblastic
- Lung (35%) ⇒ 20% osteoblastic
- Thyroid (60%)
- Kidney-Bladder (25%-40%)
- Stomach
- Ovary
- .....

Usually a late manifestation of cancer spread, more common in slow growing cancers (aggressive cancers kill earlier).
Bone metastases

- 85% axial skeleton
  - 40% vertebrae
  - 30% ribs and sternum
  - 10% pelvis
  - 10% scalp

- 15% long bones
Balanced Remodeling of Bone
The “Vicious Loop”

Tumor proliferation

Inflammation ⇒ pain

Disruption of normal bone remodeling

JP Vuillez, Grenoble
Bone Resorption Due to Metastasis

Osteoblasts

Metastasis
Full-Blown Skeletal Metastases

• Source of considerable morbidity: pain, hypercalcemia, compression of spinal cord, pathologic fracture, bone marrow infiltration.

• Pain initially mild to moderate, progressively increasing, to become multifocal and refractory to various treatments.
Mobility restriction
Sleep reduction

Worsening patient’s quality of life.
Pain from Bone Metastasis

• Mostly indirect stimulation of sensory nerve endings through release of cyto-kines, histamine, prostaglandins.

• Stimulation of periosteal nerve endings due to direct neoplastic involvement.

• Increased intramedullary pressure.

• Collapse of bone structure $\Rightarrow$ fracture.

• Radicular compression (spine).
Therapy of Metastatic Bone Pain

- **Effective anti-tumor therapies:**
  - chemotherapy
  - hormonal therapy
  - anti-tumor radiopharmaceuticals

- **Bisfosfonates**
- **Bone-seeking radiopharmaceuticals**

- **Palliation therapies:**
  - external beam radiation therapy
  - surgery
  - pain-killing medications
Bone-Seeking Radionuclides

- Simultaneous treatment of multiple sites.
- Ease of administration.
- Repeatability.
- Low cost.
- Integration with the other therapies.
Therapy of Metastatic Bone Pain

- Multidisciplinary approach!

- Most therapies are not competitive but rather complementary!
A: Osteoblasts
B: Metastasis

C: Deposition of $^{153}\text{Sm}$-EDTMP
Mechanisms of Bone Pain Palliation by Ionizing Radiations

# Bone-Seeking Radionuclides for Painful Skeletal Metastases

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory pain.</td>
<td>Absolute (<em>life expectancy</em>):</td>
</tr>
<tr>
<td>Multifocal.</td>
<td>Pregnancy/Breast-feeding</td>
</tr>
<tr>
<td>Hot-spot bone scan.</td>
<td>Relative:</td>
</tr>
<tr>
<td>Pain in hot spots.</td>
<td>Myelosuppression.</td>
</tr>
<tr>
<td>Possible association with EBRT and/or bisfosfonates and/or chemo-hormonal</td>
<td>Spinal cord compression.</td>
</tr>
<tr>
<td>therapy.</td>
<td>Impending fracture.</td>
</tr>
<tr>
<td></td>
<td>Increased risk of DIC (if Plt 60,000 - 100,000/µL).</td>
</tr>
<tr>
<td></td>
<td>Inability to comply with radiation safety procedures.</td>
</tr>
</tbody>
</table>
Bone-Seeking Radionuclides

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>$T_{1/2}$ (days)</th>
<th>Mean range (bone/soft)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{89}$Sr</td>
<td>50.5</td>
<td>1.40/2.40 mm</td>
</tr>
<tr>
<td>$^{33}$P</td>
<td>25.3</td>
<td>1.70 mm</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>14.3</td>
<td>0.05 mm</td>
</tr>
<tr>
<td>$^{117m}$Sn</td>
<td>13.6</td>
<td>0.15 mm</td>
</tr>
<tr>
<td>$^{169}$Er</td>
<td>9.4</td>
<td>0.09 mm</td>
</tr>
<tr>
<td>$^{177}$Lu</td>
<td>6.7</td>
<td>0.15 mm</td>
</tr>
<tr>
<td>$^{186}$Re</td>
<td>3.8</td>
<td>0.64/1.10 mm</td>
</tr>
<tr>
<td>$^{153}$Sm</td>
<td>1.9</td>
<td>0.32/0.60 mm</td>
</tr>
<tr>
<td>$^{188}$Re</td>
<td>0.7</td>
<td>0.25 mm</td>
</tr>
</tbody>
</table>
Higher dose-rates released by shorter-living radionuclides

- Strontium-89
- Samarium-153
Bone-Seeking Radionuclides

- Prejudices causing delayed or absent use:
  - myelosuppression.
  - high cost.

- When to best treat patients:
  - Early ➔ greatest benefit(s).
  - Late ➔ unlikely benefit(s).
Indications

Treatment of bone pain caused by:
- osteoblastic metastases or mixed osteoblastic lesions;
- primarily metastases from prostate or breast cancers, but …
- any other tumour presenting osteo-blastic lesions seen as areas of intense uptake at the bone scan (matching painful areas).
Absolute Contraindications

- Acute spinal cord compression.
- Pathological fractures.
Relative Contraindications (1)

- WBC <3.5×10⁹/L.
- Hemoglobin <90 g/L.
- Plt <100×10⁹/L.

- **Lower values can be considered:**
  - e.g., WBC ≥2.4×10⁹/L, consider CSF;
  - Plt ≥60×10⁹/L, exclude DIC.

- **Extensive bone marrow involvement (e.g., “superscan”, etc.).**
Relative Contraindications (2)

- Poor renal function (GFR <30 mL/min):
  - half dose if GFR 30-50 mL/min.
- “Chronic” spinal cord compression
  - corticosteroids.
- Life expectancy <4 weeks:
  - 1-2 weeks required for full efficacy.
  - bone-seeking radionuclides are more beneficial in patients with relatively long life expectancy!
**Common Experience Regarding Efficacy of Therapy**  
* (Pain Palliation)  

<table>
<thead>
<tr>
<th></th>
<th>Partial</th>
<th>Complete</th>
<th>Begin (weeks)</th>
<th>Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{89}\text{Sr}$</td>
<td>50-65%</td>
<td>20-25%</td>
<td>2-4</td>
<td>12-24</td>
</tr>
<tr>
<td>$^{186}\text{Re}$</td>
<td>60-75%</td>
<td>18-20%</td>
<td>1-2</td>
<td>8-12</td>
</tr>
<tr>
<td>$^{153}\text{Sm}$</td>
<td>65-75%</td>
<td>30%</td>
<td>1-3</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>
Meta-Analysis

- Complete palliation of bone pain in 25%, partial response in at least 50% of the patients.
- Palliation of bone pain appearing earlier (even <7 days) with the shorter-lived radionuclides $^{153}$Sm and $^{186}$Re (higher dose-rate).
- Variable duration of response (even for as long as 18 months).

(McQuay et al. Cochrane Database Syst Rev 2000; CD001793)
Italian Multicenter Study 1996-2004
(various cancers, n = 612)

\[
\begin{array}{ll}
\text{\textsuperscript{153}Sm-EDTMP} & 359 \\
\text{\textsuperscript{89}Sr-chloride} & 227 \\
\text{\textsuperscript{186}Re-HEDP} & 26 \\
\end{array}
\]

Complete response 29.4%
Partial response 41.5%
No response 29.1%

Precautions
EthyleneDiamineTetraMethylenePhosphonic Acid

H₂O₃P

N

PO₃H₂

H₂O₃P

N

PO₃H₂

153 Sm

5Na

O₂P - O

O₂P - O

O - PO₂

O - PO₂
Pharmacokinetics of $^{153}$Sm-EDTMP

- After an i.v. injection:
  - Rapid disappearance from the blood ($t_{1/2-\alpha}$ 5.5 min; $t_{1/2-\beta}$ 66 min).
  - 0.4 % injected dose remaining in blood at 120 min.
  - Average skeletal uptake: 56.3%-76.7%, it reflects osteoblastic metastatic burden.
  - Very high bone lesion-to-normal bone ratios (3-7).

Quadramet® Pharmacokinetics

Caucasian

% of injected dose

Time post-injection, hours

18.5MBq/kg blood
18.5MBq/kg urine
37MBq/kg blood
37MBq/kg urine
Change in AUPC-VAS

- Change From Baseline
- Week Number
- Placebo
- 18.5 MBq/kg
- 37 MBq/kg

Change in Opioid Analgesic Use

- Oral Morphine Equiv./Day

Week Number

Oral Morphine Equiv./Day

0 1 2 3 4

0 15 30 45

-30 -15 0

Placebo
37 MBq/kg
Hemoglobin Levels
Placebo Controlled Studies

Hemoglobin (g/dL)

Week Number

Placebo
0.5 mCi/kg
1.0 mCi/kg
Platelet Counts
Placebo Controlled Studies

Platelets (x10^3/uL)

Week Number

0.5 mCi/kg
1.0 mCi/kg
White Blood Cell Counts
Placebo Controlled Studies

- Placebo
- 0.5 mCi/kg
- 1.0 mCi/kg

Week Number

WBCs (x10^3/μL)
Quadramet® Safety

- Mild, reversible myelotoxicity.
- It occurs at a predictable time and level, with a rapid recovery:
  - Time: WBC and platelet counts reach a nadir by 3-5 weeks after administration, then return to pretreatment levels by week 8.
  - Level: myelosuppression is generally mild-to-moderate. WBC and platelet nadirs were toxicity grade 1-2 in >90% of patients.

Repeat treatments are therefore possible, at adequate intervals.
Safety and efficacy of repeat administration of $^{153}\text{Sm}$-EDTMP to patients with metastatic bone pain (Sartor et al. Cancer 2007; 109:637-43)

- 202 patients at 22 sites in the US, Canada, and Europe.
- Multiple doses administered to 55 patients based on recurrence of bone pain.
- 134 doses administered to 55 patients:
  - 55 patients – 2 doses
  - 11 patients – 3 doses
  - 4 patients – 4 doses
  - 2 patients – 6 doses
  - 1 patient – 11 doses
Baseline and Nadir Levels of WBCs and Platelets

WBCs

Baseline
Nadir

PLTs

Baseline
Nadir

Sartor et al. Cancer 2007
Retreatment

- In responding patients when pain recurs.
- Quality of response may decrease.
- Haematological parameters must have recovered:
  - 8 weeks for $^{153}$Sm-EDTMP.
  - 6-8 weeks for $^{186}$Re-HEDP.
  - 12 weeks for $^{89}$Sr-Cl.
Cost-Effectiveness of $^{153}$Sm-EDTMP in Patients with Metastatic Prostate Cancer

- Decision-tree model for the cost of pain control over 4 months.
- Current therapy patterns based on consensus opinion of a panel of experts.
- Cost of pain control:
  - €12,515/patient for conventional therapy;
  - €5,595/patient for $^{153}$Sm-EDTMP.
- $^{153}$Sm-EDTMP as a dominant therapy in terms of incremental cost-effectiveness.

(Velasco Latras et al. Clin Transl Oncol 2005;7:198-204)
Bone seeking radiopharmaceuticals

Competition in bone uptake???
Zoledronic acid and $^{153}$Sm-EDTMP

Patients with hormone refractory prostate cancer

<table>
<thead>
<tr>
<th>SCREENING</th>
<th>TREATMENT PERIOD</th>
<th>FOLLOW UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEKS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>Z+S</td>
</tr>
</tbody>
</table>

STUDY PERIOD

$S = ^{153}$Sm-EDTMP 18.5 MBq/kg

$SM = ^{153}$Sm-EDTMP 37 MBq/kg

$Z = $Zoledronic acid 4 mg

### Urinary Excretion of $^{153}$Sm-EDTMP

<table>
<thead>
<tr>
<th>Week</th>
<th>No. of patients</th>
<th>Dose of $^{153}$Sm-EDTMP</th>
<th>Zoledronic acid (4 mg)</th>
<th>Urinary excretion of radioactivity (% of baseline ± 1 SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>18</td>
<td>18.5 MBq/kg</td>
<td>no</td>
<td>Baseline</td>
</tr>
<tr>
<td>Week 3</td>
<td>15</td>
<td>18.5 MBq/kg</td>
<td>Yes (1x)</td>
<td>100.4 ± 11.9% * (median: 97.1)</td>
</tr>
<tr>
<td>Week 15</td>
<td>12</td>
<td>37 MBq/kg</td>
<td>Yes (4x)</td>
<td>103.2 ± 10.2% * (median: 102.8)</td>
</tr>
</tbody>
</table>

* No significant difference

Change in Lesion Uptake W3 vs W1

Conclusion

• Combined therapy with $^{153}$Sm-EDTMP and Zoledronic acid is feasible and safe.

• Competition was not found in uptake of the bone-seeking agent at the lesion sites.