Radionuclide Therapy of Bone Metastases: Past, Present, Future

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Prostate Cancer Clinical States

Clinically Localized Prostate cancer

Biochemically Relapsed Prostate cancer

Non-metastatic, Hormone-responsive Prostate cancer

Non-metastatic CRPC

Metastatic, Hormone-responsive Prostate cancer

Metastatic CRPC

Chemo-refractory CRPC

Prostate cancer-specific death

Death from co-morbidities

10 - 15 years +

>200,000

60,000

>30,000

Prostatectomy
Radiation ± ADT
Brachytherapy
Primary ADT
Active Surveillance

Salvage
Radiation
Progress in Prostate Cancer

ADVANCED PROSTATE CANCER

1941: Orchietomy
1976: LHRH
1980: Mitoxantrone
1996: Docetaxel, Zoledronic acid
2004: Cabazitaxel, Sipuleucel-T
2010: Enzalutamide
2011: Denosumab
2012: Radium 223
Spectrum of Bone Disease in Prostate Cancer

- Treatment-Related Fractures
- New Bone Metastases
- Disease-Related Skeletal Complications

Castrate sensitive, nonmetastatic
Castrate resistant, nonmetastatic
Castrate resistant, metastatic
Clinical Disease States

Hormone Sensitive

- Newly diagnosed Localized disease
- Non-metastatic, Biochemical relapse
- Metastatic Hormone-naive

Castration Resistant

- Non-metastatic
- Metastatic, Asymptomatic (chemotherapy naïve)
- Metastatic, Symptomatic (chemotherapy naïve)
- Metastatic, Post docetaxel

- Ketoconazole
- Nilutamide
- Estrogens
- Provenge
- Abiraterone
- Taxotere
- Cabazitaxel
- Enzalutamide
- Alpharadin
$^{85}\text{Sr}$ (circa 1966)  $^{18}\text{F}$ (circa 1970)  $^{87m}\text{Sr}$ (circa 1974)  $^{99m}\text{Tc}$ (circa 1974)


MIPS
Molecular Imaging Program at Stanford

Stanford University
School of Medicine
Department of Radiology
Dynamic $^{18}$F NaF PET

Diagnostic $^{18}$F NaF PET
DJD  Single metastasis  Multiple metastases
Introduction

Past

Present

Future
Targeted
Radionuclide
Therapy
Targeted Radionuclide Therapy → Treatment of benign or malignant lesions
Targeted Radionuclide $\rightarrow$ Use of radiation to destroy lesions

Therapy $\rightarrow$ Treatment of benign or malignant lesions
Targeted → Delivery of radiation to specific tissue

Radionuclide → Use of radiation to destroy lesions

Therapy → Treatment of benign or malignant lesions
Targeted Radionuclide Therapy

Katie Walker, Lawrence Livermore National Lab
Choice of Carrier

Liposomes filled with radionuclides

Radiolabelled antibodies

Radiolabelled antibody fragments & various proteins

Radiolabelled peptides

Radiolabelled low molecular weight drugs

Radioactive ions

MW

$10^2$

$10^3$

$10^4$

$10^5$

$10^6$
Penetrating Distances

- Alpha
- Beta
- Gamma and X-rays
- Neutron
The ideal agent for painful bone metastases:

- More uptake in lesions than normal bone
- Distribution predicted by Tc-99m MDP scan
- Rapid clearance from remainder of body
- Long half life
- Beta energy >0.8 MeV - < 2.0 MeV
- Easy to produce
- Cost reasonable

# Nuclear Medicine: Therapy

## Radiopharmaceuticals

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>$T\frac{1}{2}$</th>
<th>MaxB (Mev)</th>
<th>Max Range (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{89}$Sr</td>
<td>50.5</td>
<td>1.46</td>
<td>6.7</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>14.3</td>
<td>1.71</td>
<td>8</td>
</tr>
<tr>
<td>$^{153}$Sm</td>
<td>1.95</td>
<td>0.8</td>
<td>3.4</td>
</tr>
<tr>
<td>$^{186}$Re HEDP</td>
<td>3.8</td>
<td>1.07</td>
<td>4.7</td>
</tr>
</tbody>
</table>
Introduction

Past

Present

Future
Past: $^{32}$P Sodium Phosphate

- Careful, do not confuse with $^{32}$P Chromic Phosphate (used for intracavitary administration)

- $^{32}$P Sodium Phosphate is for i.v. administration

- FDA-approved prior to Jan 1, 1982 for Mallinckrodt

- It is usually not administered for the treatment of bone metastases when the leukocyte count is below 5,000/ cu mm and platelet count is below 100,000/cu mm
Marketed by Anazao Health since June 2012

- Very infrequently used for painful bone metastases
- There is perception that bone marrow suppression is more common than with other radiopharmaceuticals
- Bound to hydroxyapatite
- Excretion mainly renal
- Main use in hematological diseases
  - Thrombocytopenia
  - Polycythemia vera
- Historically used for bone metastases and leukemia
Ø Introduction

Ø Past

Ø Present

Ø Future
Present: $^{89}\text{Sr}$ (Metastron®)

- Pure beta emitter
- Half-life 50.5 days
- Calcium analogue
- $^{85}\text{Sr}$ and $^{87m}\text{Sr}$ produce scans similar to $^{99m}\text{Tc}$ MDP scans
- Excretion mostly renal
Present: $^{89}$Sr (Metastron®)

- 4 mCi fixed dose
- FDA-approved in Jun, 1993 for Amersham Health (now GE Healthcare)
Present: $^{153}\text{Sm}$ (Quadramet®)

- Complex decay
- Beta has maximum energy of 0.81 keV
- Half-life 1.95 days
- Gamma photon (103 keV) can be used for imaging
- Excretion mostly renal
Present: $^{153}$Sm (Quadramet®)

- 1 mCi/Kg
- FDA-approved in March 1997 for DuPont Merck
- Now marketed by Jazz Pharmaceuticals in the US and IBA worldwide
Contraindications:

- White count <2,500
- Platelet count <60,000 (higher if falling)
- Impending cord compression
- Impending pathological fracture
- Disseminated coagulopathy
- Extensive soft tissue metastases
- Death imminent (life expectancy should be > 3-6 months)
- Within 1 month of myelosuppressive chemotherapy
Methods:

- Review indications and requirements
- Discussion with patient
- Discussion with referring physicians
- Radiation safety issues
- Follow-up arrangements
- Complications
- Re-treatment
Check list:

- Proven bone metastases
- Objective evidence of referral for therapy
- Complete blood count
- Recent bone scan
- Signed consent form
- Appropriate continuity of care, including blood counts
## Nuclear Medicine: Therapy

<table>
<thead>
<tr>
<th>Dates</th>
<th>No of papers</th>
<th>No of patients</th>
<th>%Responding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974-83</td>
<td>9</td>
<td>190</td>
<td>77 (42-90)</td>
</tr>
<tr>
<td>1985-96</td>
<td>18</td>
<td>962</td>
<td>74 (45-91)</td>
</tr>
</tbody>
</table>

About 20% can stop analgesics

A proportion have a worsening before improvement

*After McEwan Semin Nucl Med 1997*
50 males with prostate carcinoma and 26 females with breast cancer were treated.

- Good response in 64%, partial in 25%, and no response in the remaining 11% with prostate cancer.
- Good response in 62%, partial in 31%, and no response in the remaining 8% with breast cancer.
- Duration of the response: 3 - 12 months (mean 6 months).
- Retreatment was as effective.

A decrease in the initial leucocyte and platelet counts after the 1st month of treatment, with a gradual recovery within 6 months.
Palliative treatment was given to 131 patients in the form of local radiotherapy (n=10), $^{89}$Sr (n=46) or i.v. olpadronate (n=66)

The incidence of SCC was 17% in the whole group, and highest in controls receiving no palliation (50%)

None of the patients treated with local radiotherapy, only 4% of patients receiving $^{89}$Sr and 21% of patients given olpadronate developed this complication
64 patients with painful bone metastases treated with $^{153}$Sm were retrospectively evaluated.

The most common primaries were breast in 28 cases (44%) and prostate in 27 (41%).

The response rate was 85% (21% complete, 40% moderate, and 24% minor).

Onset of improvement took place a median of 7 days after $^{153}$Sm administration, and pain relief persisted for a mean of 3 months.

Myelotoxicity appeared in 29% of the administrations.
43 prostate cancer patients with bone metastases were given consolidation docetaxel 20 mg/m\(^2\)/wk for 6 weeks and \(^{153}\text{Sm}\) (37 MBq/kg) during week 1.

A PSA response was obtained in 77\% (95\% CI, 61\% to 82\%).

The pain response rate was 69\% (95\% CI, 49\% to 85\%).

Although a serum PSA relapse eventually occurred in all patient cases, this regimen resulted in pain control in the long-term.
60 male patients with advanced prostate carcinoma and 40 female patients with advanced breast carcinoma

30 men and 20 women were treated with $^{89}$Sr

30 men and 20 women were treated with $^{153}$Sm

Complete pain relief was found in 40% of women and 40% of men treated using $^{153}$Sm and in 25% of women and 33% of men treated with $^{89}$Sr

No analgesic effect occurred in 20% of patients

A better analgesic effect was found in cases of osteoblastic metastases compared to mixed metastases
Bone marrow recovery following use of systemic $^{153}$Sm-lexidronam and $^{89}$Sr-chloride for bone pain palliation after myelosuppressive therapy


FRANK J. PAPATHEOFANIS$^1$ & MOHAMMAD M. NAJIB$^2$

- 48 patients with solid tumors who failed multi-agent chemotherapy were investigated
- In patients who received $^{153}$Sm, there is a spike in FL$^*$ concentration at approximately 3 weeks after dose administration preceding a decrease in WBC and PLT counts
- A spike in FL levels in patients who received $^{89}$Sr therapy is noted at approximately 10 weeks ($p < 0.034$)
- Changes associated with $^{153}$Sm therapy occurred earlier and returned to control levels more rapidly than did those in patients similarly treated with $^{89}$Sr

*FL = plasma flt3 ((FMS (Friend murine strain))-like tyrosine kinase 3)-ligand cytokine
A retrospective analysis of the cost effectiveness of treatment with Metastron® (^{89}Sr-chloride) in patients with prostate cancer metastatic to bone

Aim: to estimate the cost of medical care for patients on \(^{89}\)Sr as adjunct therapy in patients with prostate cancer metastatic to bone and to compare the costs of those receiving \(^{89}\)Sr with those receiving placebo

The group receiving \(^{89}\)Sr had a lifetime reduction of $1,720 per person when compared with placebo

A reduction of $5,696 per patient in the \(^{89}\)Sr group was shown based upon requirements for admission for tertiary care
- Introduction
- Past
- Present
- \textit{Future}
Future: $^{223}\text{Ra}$ (Alpharadin$^\text{®}$)

- Complex decay scheme, including mostly alpha, but also beta and gamma
- Half life of 11.4 days
- Excretion mostly renal, but also through the GI tract
- Very short range and therefore causes less damage to surrounding tissues than other radiopharmaceuticals
Future: $^{223}$Ra (Alpharadin®)

- 50 kBq/kg

- Developed in Norway by Algeta, approved in Europe

- Marketed by Bayer Healthcare
**Alpha Particle Radiation**

- **Daughter Nucleus**: Th-231
- **Parent Nucleus**: U-235
- **Alpha Particle**: (Helium Nucleus)
Future: $^{223}\text{Ra}$ (Alpharadin\textsuperscript{®})

- Self-targets to bone metastases by virtue of its properties as a calcium-mimic

Properties of selected radiopharmaceuticals for treatment of bone metastases in mCRPC

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Particle</th>
<th>Primary excretion</th>
<th>Physical half-life (days)</th>
<th>Particle energy in MeV</th>
<th>Tissue range (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radium-223 ((\text{Alpharadin}^{\text{R}})_{38})</td>
<td>Alpha</td>
<td>Small bowel</td>
<td>11.4</td>
<td>5.56</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Samarium-153 ((\text{Quadramet}^{\text{R}})_{76}^{*})</td>
<td>Beta</td>
<td>Kidney</td>
<td>1.9</td>
<td>0.81</td>
<td>3</td>
</tr>
<tr>
<td>Strontium-89 ((\text{Metastron}^{\text{R}})_{77}^{*})</td>
<td>Beta</td>
<td>Kidney</td>
<td>50.5</td>
<td>1.46</td>
<td>8</td>
</tr>
</tbody>
</table>


**Decay of** \(^{223}\text{Ra}\):
- 95.3% emitted as \(\alpha\) particles
- 3.6% emitted as \(\beta\) particles
- 1.1% emitted as photons
Radium-223 chloride: a potential new treatment for castration-resistant prostate cancer patients with metastatic bone disease

- **Phase II**: Found no significant side effects and showed 4.5 months increased OS, delayed SREs, and improvement in biochemical end points (PSA, total ALP)

- **Phase III**: Alpharadin successfully met the primary endpoint of OS in the ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer patients) study in 922 patients
ALSYMPCA Trial Results

- $^{223}$Ra improved overall survival by 44% compared to placebo ($p = 0.00185$)

- Average overall survival was 14.0 months for men treated with $^{223}$Ra and 11.2 months for men treated with placebo

- Average time to first skeletal-related event was 13.6 months for men treated with $^{223}$Ra and 8.4 months for men treated with placebo

- Levels of total alkaline phosphatase (ALP) were normalized in 33% of men treated with $^{223}$Ra and 1% of men treated with placebo

- Treatment with $^{223}$Ra improved time to PSA progression by 49% compared to placebo ($p = 0.00015$)
ALSYMPCA Trial Results

**A. Overall Survival**
- 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)

**B. Time to First Symptomatic Skeletal Event**
- Hazard ratio, 0.66 (95% CI, 0.52–0.83)
- P<0.001
- Radium-223 (median time to first symptomatic skeletal event, 15.6 mo)
- Placebo (median time to first symptomatic skeletal event, 9.8 mo)
## ALSYMPCA Trial Results

### Table 2. Main Secondary Efficacy End Points in the Intention-to-Treat Population.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Radium-223 (N=614)</th>
<th>Placebo (N=307)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to first symptomatic skeletal event — mo</td>
<td>15.6</td>
<td>9.8</td>
<td>0.66 (0.52–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to increase in total alkaline phosphatase level — mo</td>
<td>7.4</td>
<td>3.8</td>
<td>0.17 (0.13–0.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to increase in PSA level — mo</td>
<td>3.6</td>
<td>3.4</td>
<td>0.64 (0.54–0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with ≥30% reduction in total alkaline phosphatase response — no./total no. (%)</td>
<td>233/497 (47)</td>
<td>7/211 (3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Patients with normalization of total alkaline phosphatase level — no./total no. (%)*</td>
<td>109/321 (34)</td>
<td>2/140 (1)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

* Only patients who had elevated total alkaline phosphatase levels at baseline are included.
Common non-hematologic adverse events (occurring in at least 15% of patients) included:

- Bone pain (in 43% of $^{223}$Ra patients vs. 58% of placebo-treated patients)
- Nausea (34% vs. 32%)
- Diarrhea (22% vs. 13%)
- Constipation (18% vs. 18%)
- Vomiting (17% vs. 13%)

The most common hematologic adverse event was anemia (in 27% of $^{223}$Ra patients vs. 27% of placebo-treated patients)

The most common grade 3 and grade 4 adverse event was bone pain (18% of $^{223}$Ra patients vs. 23% of placebo-treated patients)
Radiation/Release Considerations

- Since patients treated with Alpharadin® emit negligible external radiation doses, they can be released immediately.
- For example, the average patient receiving 3.5 MBq (95 µCi) would have a dose rate at 1 m < 0.35 μSv/h (0.035 mrem/h).
- There are no restrictions on family contact after administration of Alpharadin®.
- The range of α-particles in human tissue is approximately 0.1 mm.
- Once injected, α-particles are stopped by the patient’s tissue.
THANK YOU!

http://nuclearmedicine.stanford.edu

http://mips.stanford.edu