Treatment of Prostate Cancer with Radionuclide Based Therapies.

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Outline
- Background Prostate Cancer Treatment.
- Palliation with beta emitters.
- Improving survival with alpha emitters.
- Imaging for therapy and response evaluation.
- Future directions.

Prostate Cancer
- Most common cancer in men, second deadliest.
- Risk stratification guides therapy
  - TNM stage, biopsy (e.g. Gleason/(+) cores), PSA etc.
- Metastatic Castrated Resistant Prostate Ca (mCRPC)
  - Androgen deprivation/hormone Rx resistance
  - Multiple therapies: Androgen pathway (abiraterone acetate); Microtubules (docetaxel) Immunotherapy (sipuleucel-T); Alpha emitting radionuclide (Ra-223).

mCRPC Bone Metastases
- >90% have bone metastases
- Symptomatic Skeletal Events:
  - pathologic fractures, spinal cord compression
  - Palliative Rx:
    - External beam radiotherapy: 8 Gy single dose
    - Sr-89 CI2, Sm-153 EDTMP -
  - Main cause of death in mCRPC

Bone Seeking Radionuclides
Mechanism of uptake
- Calcium analogs
  - Sr-89 CI*
  - Ra-223 dichloride*
- Attached to phosphate
  - Sm-153 EDTMP*
  - Rh-186/188 HEDP
  - Lu-177 EDTMP
  - Sm-117mDTPA
  - P-32

*FDA approved agents
**Decay and Marrow/Bone Ratios Clinically Useful Bone-seeking Isotopes**

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life days</th>
<th>Bone surface to red marrow</th>
<th>Particle</th>
<th>Emission energy MeV</th>
<th>Range (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{153}$Sm-EDTMP</td>
<td>2</td>
<td>4.4</td>
<td>Beta</td>
<td>0.66 max</td>
<td>0.6</td>
</tr>
<tr>
<td>$^{89}$SrCl$_2$</td>
<td>50.5</td>
<td>1.6</td>
<td>Beta</td>
<td>0.58</td>
<td>2.4</td>
</tr>
<tr>
<td>$^{223}$RaCl</td>
<td>11.4</td>
<td>10.3</td>
<td>Alpha</td>
<td>27.4</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

*Clin Cancer Res 2006; 12(20Suppl) October 15, 2006*

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**Comparison of Alpha and Beta Particles from Bone-Seeking Cancer Drugs**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Alpha</th>
<th>Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range (um)</td>
<td>40-90</td>
<td>50-6000</td>
</tr>
<tr>
<td>LET; keV/mm</td>
<td>60-230</td>
<td>0.015-0.4</td>
</tr>
<tr>
<td>Relative mass</td>
<td>7000</td>
<td>1</td>
</tr>
<tr>
<td>DNA hits to kill a cell</td>
<td>1-5</td>
<td>100-3000</td>
</tr>
<tr>
<td>Cytotoxic against G$_0$ cells</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Effective against “radio-resistant” cells</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

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**$^{89}$Sr Chloride**

- Indication: palliation of painful skeletal mets
- $T_{1/2}$ 50d, Dose 4.0 mCi I.V., calcium analog, excretion renal (80%); GI (20%)
- Response rate: 60-84%  
  -Pts. w/moderate pain; reasonable life expectancy  
  -Transient reduction in blood counts

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**$^{89}$Sr Chloride**

- “Flare” – good response
- Can retreat at 90 days
- Enhanced relief w/concurrent chemotherapy
- Delayed onset of new sites of pain
- No survival benefit/+chemo (10.8 mCi doses)  
  - Cancer. 2015 Jan 1;121(1):69-76.
**153Sm-EDTMP for pain palliation**
- Indication: palliation of painful bone mets
- Distribution like bone seeking agents (MDP)
  - $T_{1/2}$ 2 days, Imaging Post Rx (103 keV gamma, 28%)
- Dose = 37 MBq/kg (1 mCi/kg)
  - Platelet nadir: 16 and 45 days (median 28 d)
  - BM suppression mild, reversible, no Grade IV
  - No survival benefit when combined with chemo

**Utility of Ra-223 dichloride**
- Convenient half-life (11.4 days)
- Inherent bone-seeking biodistribution
- Potent DNA-damaging property

**Biodistribution Ra-223**
- Rapid blood clearance
- Early uptake in the small bowel
- Fecal clearance
- Little urinary excretion
- No significant organ redistribution
- Bone retention is long

**Alpha emitter Ra-223 and Survival in Metastatic Prostate Cancer**

**Main Secondary Efficacy End Points in the Intention-to-Treat Population.**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Ra-223 (N=113)</th>
<th>Placebo (N=110)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first symptomatic skeletal event—mo</td>
<td>23.5 (12.7, 32.2)</td>
<td>24.0 (12.0, 35.3)</td>
<td>0.93 (0.56–1.54)</td>
<td>0.801</td>
</tr>
<tr>
<td>Time to increase in total alkaline phosphatase level—mo</td>
<td>6.1 (2.6, 11.6)</td>
<td>6.1 (2.6, 11.6)</td>
<td>1.00 (0.57–1.75)</td>
<td>0.980</td>
</tr>
<tr>
<td>Time to increase in PSA level—mo</td>
<td>3.2 (1.5, 5.5)</td>
<td>3.2 (1.5, 5.5)</td>
<td>1.00 (0.55–1.82)</td>
<td>0.980</td>
</tr>
<tr>
<td>Patients with a 50% reduction in total alkaline phosphatase—mo</td>
<td>100/113 (89%)</td>
<td>100/113 (89%)</td>
<td>1.00 (0.59–1.71)</td>
<td>0.999</td>
</tr>
<tr>
<td>Patients with normalization of total alkaline phosphatase—mo</td>
<td>100/113 (89%)</td>
<td>100/113 (89%)</td>
<td>1.00 (0.59–1.71)</td>
<td>0.999</td>
</tr>
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*Only patients who had elevated total alkaline phosphatase levels at baseline are included.*
FDA Approval Summary:
Radium 223 Dichloride
• Large (921 patients), prospective, randomized, placebo-controlled, phase III study
• Best supportive care in the two study groups, with overall survival as the primary end point.
• Treatment effect confirmed via multivariate analysis
• First alpha-emitting radiopharmaceutical to demonstrate an OS advantage in metastatic prostate cancer.


Patient selection
• Castration Resistant Prostate Cancer
• Symptomatic osseous metastatic disease
  – Bone scan required
• No known visceral metastatic disease
  – Visceral: Lung, liver, brain
  – Non-Visceral: LN(<4cm), prostate bed, bladder

Laboratory evaluation
• Monitor blood counts at baseline and prior to every dose
• Prior to first administering:
  – Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L
  – Platelet count ≥ 100 × 10^9/L
  – Hemoglobin ≥ 10 g/dL
• Prior to subsequent administrations:
  – ANC ≥ 1 × 10^9/L
  – Platelet count ≥ 50 × 10^9/L
• Discontinue if hematologic values do not recover within 6 to 8 weeks after the last administration

Phase I and II toxicity
• < 1% of 292 patients treated in phase I & II trials receiving between 5 and 250 kBq of Ra-223 had CTC grade IV hematologic toxicity; 2%-4% had grade III toxicity.
• α-emitter mostly on bone
• surface and disease sites
  – Exposure rates to staff is low

Outpatient Therapy
• Dose: 50 kBq (1.35 uCi)/kg, I.V.
• 4 week intervals for 6 IV injections.
• Adverse reactions
  – Nausea, diarrhea, vomiting, peripheral edema
• Hematologic abnormalities
  – Thrombocytopenia
• Recent studies showed it is well tolerated irrespective of previous docetaxel use
  – Lancet Oncology, 15, No. 12, p1397–1406, November 2014
Discuss with patient

- Goal: Improve survival and quality of life
- Side effects (infrequent)
  - Blood counts, GI symptoms, Flare
- Radiation precautions (universal)
  - Good hand hygiene esp after bowel movement
  - Others avoid contact with body fluid or contaminated material
  - Condom use for 1 week after injection
  - no restrictions for returning to normal activities, contact with family and public, etc.

Skeletal Tumor Burden Assessment with Fluoride PET/CT

- TLF10 = 2,729 TLF10 = 110
- TLF10 = 8,389 TLF10 = 5,576 TLF10 = 898

Overall Survival according to TF10 on Fluoride PET/CT

Determination of Skeletal Tumor Burden on 18F-Fluoride PET/CT.

- 98 patients, 158 fluoride PET/CT scans
- Whole-body segmentation method
- Semi-automated measurements of TLF10 and FTV10 exhibited high inter-observer reproducibility
- Potential for assessing total disease burden and therapy response in patients with predominantly osteoblastic skeletal metastases.

110 patients treated with 532 cycles of Ra-223 dichloride

- On multivariable analysis, patients treated with full 6 cycles and abiraterone were significantly associated with OS and PFS.
- Patients treated 6X and EBRT remained significantly associated with BMF.
Skeletal Tumor Burden on Baseline 18F-Fluoride PET/CT Predicts Bone Marrow Failure After 223Ra Therapy.

- 41 patients, MCRP
- Significantly increased risk of developing BMF in patients with TLF10 of 12,000 or greater.
- In multivariable analysis, TLF10 was the only independent predictor of BMF (HR, 6.66; P = 0.0237).
- 223Ra was beneficial and reduced the risk of death even in patients with a high skeletal tumor burden.
- Fluoride PET/CT is able to determine which patients will benefit from 223Ra and which will develop BMF.


18F-PET/CT Predicts Bone Marrow Failure After 223Ra Therapy.

Patients A and B were still alive and did not develop BMF. Patients C and D deceased. C, TLF10 = 8768 and FTV10 = 440, died without developing BMF. D, TLF10 = 25841 and FTV10 = 1569, died with BMF.


Phase I Dose Escalation of Monthly Intravenous Ra-223 dichloride in Osteosarcoma

- MTD of monthly Ra-223-radium dichloride
- Comparison of safety and toxicity of 50, 75, and 100 kBq Ra-223-radium dichloride /kg.
- Compare alkaline phosphatase reduction to $^{99m}$Tc-MDP, $^{18}$FDG-PET-CT, $^{18}$FNa PET-CT scans to determine objective response.

Interim analysis

- 18 patients with OS treated with Ra-223Cl2
- Cumulative doses: 6.84 MBq to 57.81 MBq
- Imaging with MDP, FDG, and NaF PET/CT
- Mixed response: bone forming lesions respond, soft tissue/lung lesions progress
- NaFCIST criteria: tool for response evaluation
Radium-223 dichloride in advanced breast cancer with bone-dominant disease

- 23 patients, phase IIIa non-randomized, safety efficacy
- 50 kBq/kg IV every 4 weeks, 4 cycles, FDG PET/CT
- Reduced serum bALP, urinary N-telopeptide of type 1
- 150 lesions, 32% PET response (wk 9), 41% (wk 17)

Breast Cancer Res Treat. 2014 Apr 13

Summary

- Effective palliation with Sr-89 and Sm-153.
- Ra-223 provides survival/symptom benefits.
- Imaging can assess extent of disease, provides response and prognostic information
- Apply beta and alpha emitters for other tumors and potentially more effective therapy.