Targeted Alpha Particle Therapy: Imaging, Dosimetry and Radiation Protection

Michael Lassmann
Targeted Therapy – Basic Principles

- **β-Particle**
  - Range: 800-5000 μm
  - LET: 0.8 keV/μm

- **α-Particle**
  - Range: 40-90 μm
  - LET: 100 keV/μm

Diagram showing the interaction of particles with normal tissue and tumor.
Influence of the particle type

0.01 Gy gamma photons
   50 ± 7 electron tracks per cell (on average)

0.01 Gy alpha
   dose spectrum, from 0 to 0.30 Gy
   mean hit number: 0.1
   90% of cells are spared!

(Goodhead in *Dosimetry of ionizing radiations*, Kaze, Bjarngard and Attix ed., Orlando1987)
DNA damage caused by the track of an alpha particle through a human lymphocyte visualized by the γ-H2AX assay

(Image courtesy of H. Scherthan, Bundeswehr Institute of Radiobiology, Munich, Germany)
Chromosome Aberrations after $^{224}$Ra Therapy

Treatment for Ankylosing Spondylitis

Total administered activity: 10 MBq

Alpha emitting isotopes for therapeutic applications in nuclear medicine

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-Life</th>
<th>Max. Particle Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>At-211</td>
<td>7.2 hrs</td>
<td>6.0 MeV</td>
</tr>
<tr>
<td>Bi-213</td>
<td>46 min</td>
<td>6.0 MeV</td>
</tr>
<tr>
<td>Ra-223</td>
<td>11.4 days</td>
<td>5.8 MeV</td>
</tr>
<tr>
<td>Ac-225</td>
<td>10.0 days</td>
<td>5.9 MeV</td>
</tr>
</tbody>
</table>
Therapy Modalities (Generic Use)

Metabolic active radiopharmaceuticals
- Radioiodine Therapy of Thyroid Diseases (benign/malignant) ($^{211}$At in-vitro studies)
- Bone Pain Palliative Treatment of Bone Metastases ($^{223}$Ra)

Specifically binding radiopharmaceuticals
- Radiopeptide therapy (addressing specific antigens or receptors) ($^{213}$Bi, $^{225}$Ac)
- Treatment of lymphoma using antibodies ($^{212}$Pb)

Locoregional therapies
- Selective Internal radiotherapy (Alpha Emitter: possible option?)
Radium

**$^{223}$Ra - Phase III Randomised Trial (ALSYMPCA)**

- **N = 921**
- **0.05 MBq/kg**
Decay of Ra-223

Ra-223 → Rn-219 → Po-215 → Pb-211 → Bi-211 → Tl-207 → Pb-207

Ra-223 → Rn-219 → Po-215 → Pb-211 → Bi-211 → At-215 → Bi-211 → Tl-207 → Pb-207

Pb-209 → Bi-209

11.435 d, 1.781 ms, 3.96 s, 36.1 m, 2.14 m, 4.77 m, 0.516 s, stable
# Decay of Ra-223

<table>
<thead>
<tr>
<th>Decay Chain</th>
<th>Branching Ratio</th>
<th>Half-life</th>
<th>Alpha and Recoil Nuclei (MeV)</th>
<th>Beta and Auger Electrons (MeV)</th>
<th>Gamma and X-Rays (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ra-223</td>
<td></td>
<td>11.43 days</td>
<td>5.77</td>
<td>0.078</td>
<td>0.141</td>
</tr>
<tr>
<td>Rn-219</td>
<td>100%</td>
<td>3.96 s</td>
<td>6.88</td>
<td>0.007</td>
<td>0.059</td>
</tr>
<tr>
<td>Po-215</td>
<td>100%</td>
<td>1.78 ms</td>
<td>7.49</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Pb-211</td>
<td>100%</td>
<td>36.10 min</td>
<td>-</td>
<td>0.454</td>
<td>0.064</td>
</tr>
<tr>
<td>Bi-211</td>
<td>100%</td>
<td>2.14 min</td>
<td>6.66</td>
<td>0.010</td>
<td>0.047</td>
</tr>
<tr>
<td>Ti-207</td>
<td>99.7%</td>
<td>4.77 min</td>
<td>-</td>
<td>0.494</td>
<td>0.002</td>
</tr>
<tr>
<td>Po-211</td>
<td>0.3%</td>
<td>0.52 s</td>
<td>7.61</td>
<td>0.000</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Imaging: gamma spectroscopy of Ra-223

HPGe

Nal
Gamma Camera
Gamma Camera

Spatial Information

Energy Information

Patient XXX
* 11-Nov-1966
Study 123
11-Nov-2011

Uptake:
22 %
Biodistribution of Ra-223

Quantitative imaging of $^{223}\text{Ra}$-chloride (Alpharadin) for targeted alpha-emitting radionuclide therapy of bone metastases

Cecilia Hindorf, Sarah Chittenden, Anne-Kirsti Aksnes, Chris Parker, and Glenn D. Flux
Biodistribution of Ra-223

Phase I pharmacokinetic and biodistribution study with escalating doses of $^{223}$Ra-dichloride in men with castration-resistant metastatic prostate cancer

Jorge A. Carraquillo · Joseph A. O’Donoghue · Neeta Pandit-Taskar · John L. Humm · Dana E. Rathkopf · Susan F. Nislin · Matthew J. Williamson · Kristine L. Almén · Anne-Kirsti Akeson · Steven M. Larson · Howard I. Scher · Michael J. Maeris
Biodistribution of Ra-223

Phase I pharmacokinetic and biodistribution study with escalating doses of $^{223}$Ra-dichloride in men with castration-resistant metastatic prostate cancer


Fig. 1 Decay-corrected percentage of $^{223}$Ra retained in the whole body (initial pre-void counts taken as 100 %) in patients ($n=8$) over a period of approximately 1 week post-administration
# Nuclear Medicine Dosimetry

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low activities ~&lt;1GBq, short-lived nuclides, γ/β⁺ emitters</td>
<td>High activities ~&gt;1GBq for beta emitters, &gt; 10MBq for alpha emitters</td>
</tr>
<tr>
<td></td>
<td>long-lived nuclides, α/β⁻ emitters</td>
</tr>
<tr>
<td>Stochastic risk</td>
<td>Deterministic damage and stochastic risk</td>
</tr>
<tr>
<td>Model-based dosimetry in a representative group of volunteers or patients</td>
<td>Patient-specific dosimetry</td>
</tr>
<tr>
<td>Optimize image quality</td>
<td>Maximize tumor absorbed doses</td>
</tr>
<tr>
<td>Minimizing radiation-associated risk</td>
<td>Minimize the absorbed doses to the organs-at-risk</td>
</tr>
</tbody>
</table>
Internal Dosimetry in Nuclear Medicine Therapy

- Aspects that alter the absorbed dose
  - Administered activity
  - Physical and chemical properties of the radiopharmaceutical
  - Source organs irradiate target organ/s
  - Biokinetics and biodistribution
    - Biological uptake and excretion

- Absorbed dose calculation:
  - \( MIRD^*-\text{Scheme (1976)} \)
  - Summing over all organ contributions

\[
D_T = A_0 \cdot \sum_s \int_0^\infty A_S(t') \, dt' \cdot S_{T\leftarrow S} = A_0 \cdot \sum_s \tau_s \cdot S_{T\leftarrow S}
\]
Dosimetry in Nuclear Medicine

$$D = S \cdot \int_{0}^{\infty} A(t) \, dt$$

- **MBq**
- **Days p.i.**
- **Absorbed dose rate per unit activity**
- **Number of decays (time-integrated activity coefficient)**
Dosimetry of Metastases
Dosimetry of Metastases

Mean absorbed dose after 1\textsuperscript{st} injection: 0.7 (0.2-1.9) Gy
Total RBE weighted dose (D_{RBE5}): 18.9 Gy
Fig. 4: The biokinetic model of ICRP Publication 67 for radium. The dashed arrows indicate pathways of less importance for the short-lived isotope $^{224}$Ra.

Biokinetic Modelling for Radium – ICRP 67
6 treatments for a 70 kg person with an administered activity of 0.05 MBq/kg $^{223}$Ra-chloride each (overall: 21 MBq $^{223}$Ra-chloride):

absorbed alpha dose to the bone endosteum: $\sim 16$ Gy

absorbed alpha dose to the red bone marrow: $\sim 1.5$ Gy
## Dosimetry – $^{223}$Ra

<table>
<thead>
<tr>
<th>GI tract</th>
<th>Gy/Bq Alpha</th>
<th>Gy/Bq Beta/Gamma</th>
<th>Relative Beta/Gamma Contribution [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus</td>
<td>3.2E-09</td>
<td>1.7E-10</td>
<td>5</td>
</tr>
<tr>
<td>St wall</td>
<td>3.2E-09</td>
<td>2.1E-10</td>
<td>6</td>
</tr>
<tr>
<td>SI wall</td>
<td>3.2E-09</td>
<td>3.9E-10</td>
<td>11</td>
</tr>
<tr>
<td>ULI wall</td>
<td>6.8E-09</td>
<td>1.4E-08</td>
<td>67</td>
</tr>
<tr>
<td>LLI wall</td>
<td>1.3E-08</td>
<td>4.0E-08</td>
<td>75</td>
</tr>
<tr>
<td>Colon</td>
<td>9.5E-09</td>
<td>2.5E-08</td>
<td>72</td>
</tr>
<tr>
<td>Kidneys</td>
<td>3.4E-09</td>
<td>2.4E-10</td>
<td>7</td>
</tr>
<tr>
<td>Liver</td>
<td>3.6E-08</td>
<td>1.5E-09</td>
<td>4</td>
</tr>
<tr>
<td>Muscle</td>
<td>3.2E-09</td>
<td>2.0E-10</td>
<td>6</td>
</tr>
<tr>
<td>Ovaries</td>
<td>3.2E-09</td>
<td>4.3E-10</td>
<td>12</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3.2E-09</td>
<td>2.2E-10</td>
<td>6</td>
</tr>
<tr>
<td>Red marrow</td>
<td>7.2E-08</td>
<td>5.5E-09</td>
<td>7</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET airways</td>
<td>3.2E-09</td>
<td>1.7E-10</td>
<td>5</td>
</tr>
<tr>
<td>Lungs</td>
<td>3.2E-09</td>
<td>1.9E-10</td>
<td>6</td>
</tr>
</tbody>
</table>
Radiation Protection

Measured removable contamination detection efficiencies and minimum detectable activities (MDA) of various 1 min integrated survey modalities for $^{223}$Ra wipe tests.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Background (cpm)</th>
<th>Efficiency (cpm/dpm)</th>
<th>Minimum detectable activity (dpm)</th>
<th>(Bq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha Probe (Zinc Sulfide)$^a$</td>
<td>0</td>
<td>0.08</td>
<td>71</td>
<td>1.2</td>
</tr>
<tr>
<td>Thin Window Beta/Gamma Probe (GM)$^a$</td>
<td>28</td>
<td>0.13</td>
<td>350</td>
<td>5.8</td>
</tr>
<tr>
<td>Low Energy Gamma Probe (Sodium Iodide)$^a$</td>
<td>94</td>
<td>0.29</td>
<td>1296</td>
<td>21.6</td>
</tr>
<tr>
<td>Liquid Scintillation Counter</td>
<td>49</td>
<td>0.97</td>
<td>64</td>
<td>1.1</td>
</tr>
<tr>
<td>Gamma Counter</td>
<td>210</td>
<td>0.40</td>
<td>333</td>
<td>5.6</td>
</tr>
</tbody>
</table>

$^a$For wipe test evaluations in a fixed geometry at a distance of 0.32 cm.


RADIATION SAFETY CONSIDERATIONS FOR THE USE OF $^{223}$RaCl$_2$ DE IN MEN WITH CASTRATION-RESISTANT PROSTATE CANCER

Lawrence T. Dauer$^{*,†}$, Matthew J. Williamson$, John Humm$^{*,†}$, Joseph O’Donoghue$^{*,†}$, Rashid Ghani$^{†}$, Robert Awadallah$^{†}$, Jorge Carrasquillo$^{†,‡}$, Neeta Pandit-Taskar$^{†,‡}$, Anne-Kirsti Aksnes$^{§}$, Colin Biggin$^{§}$, Vigdis Reinton$^{§}$, Michael Morris$^{*,†,‡}$, and Jean St Germain$^{*}$
## Radiation Protection – Dose Rate (µSv h⁻¹ MBq⁻¹)

<table>
<thead>
<tr>
<th>Time post administration (h)</th>
<th>0.0 m</th>
<th>0.3 m</th>
<th>1.0 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.58 (0.77)</td>
<td>0.12 (0.32)</td>
<td>0.03 (0.18)</td>
</tr>
<tr>
<td>24</td>
<td>0.91 (0.95)</td>
<td>0.12 (0.16)</td>
<td>0.03 (0.06)</td>
</tr>
<tr>
<td>48</td>
<td>0.19 (0.24)</td>
<td>0.01 (0.06)</td>
<td>0.01 (0.02)</td>
</tr>
<tr>
<td>144</td>
<td>0.05 (0.11)</td>
<td>0.01 (0.05)</td>
<td>0.01 (0.03)</td>
</tr>
</tbody>
</table>


RADIATION SAFETY CONSIDERATIONS FOR THE USE OF $^{223}$RaCl₂ DE IN MEN WITH CASTRATION-RESISTANT PROSTATE CANCER

Ra-223 was found in saliva (median: 22 Bq/g, range: 5.9-124 Bq/g) and excreted with sweat (median: 0.12 Bq/cm², range: 0.01 - 0.6 Bq/cm²) in the first 24 hours p.i.

Contaminations in restrooms and kitchens were low (median: 0.021 Bq/cm², range: < DL - 0.35 Bq/cm²)

The exposure due to inhalation of Rn-219 and its progeny for relatives staying in a room with the patient is expected to be of no concern

Wanke et al, SNMMI Abstract 2015
Radiation Protection – Extremity Surveillance

Recommended by the German BfS if more than 28 patients per year are handled by a single individual

Conclusions I

➢ Administering alpha emitters opens a promising path to a new treatment option for molecular targeted radiotherapy

➢ Ra-223-dichloride shows a benefit in survival in CRPC patients; it is administered on a per kg basis

➢ Measuring the biodistribution in patients is challenging due to the low activities administered and low emission probabilities of suitable photon energies

➢ For Ra-223 absorbed dose assessments still mostly rely on compartment modelling based on ICRP model
Conclusions II

- The RBE of treating systemically with alpha emitters is yet to be determined

- Normally, no radiation protection measures are needed beyond those needed for high-activity treatment with beta/gamma emitters. Further measures are to be considered only if the patient numbers handled by a single person exceed 25 -30
Thank you!
Data Sources for Risk Assessments for Alpha Emitters

Major Number of Treatments:

a) Spiess Cohort, „high dose“ treatment with $^{224}\text{Ra}$ (n=899)
b) Wick Cohort, „low dose“ treatment with $^{224}\text{Ra}$ (n=1588)
c) ALSYMPCA Trial with $^{223}\text{Ra}$ (n=614/921)

Other isotopes used for treatments were applied to few patients and without long-term follow-up
Cancer Induction – Spiess Cohort

- Cohort of 899 patients with several injections of $^{224}$Ra between 1945 and 1955
- Patients were treated with high doses (mean bone surface dose: 30 Gy, mean specific activity: 0.66 MBq/kg)
- Almost all of those exposed during childhood or adolescence
- Treatment mainly for either TB (455 patients including 214 children and juveniles), especially bone TB, or AS (393 patients who were mostly male adults)
- The AS patients continued were treated in the late 1950s and in the 1960s with $^{224}$Ra.