Medical Use of Radium-223 Chloride: Regulatory and Technical Considerations

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Radiobiology

- Compelling rationale for Tx of skeletal metastases
  - Calcium-mimetic = Bone-seeker → Osteoblastic lesions
  - Alpha-emitter - Several cell-diameter R
  - Hi LET & RBE

High biologically effective dose (= RBE•D) to malignant cells in bone w/ sparing of hematopoietic cells

Clinical data

- Convincing clinical data, >1,000 CRPC pts in Phase 1, 2, & 3 trials *

Safety

- Mild GI toxicity
- Mild-to-moderate myelosuppression

Efficacy

- >50% bone pain reduction
- Survival advantage

* Bayer Healthcare data
Physical Data

- $^{223}\text{RaCl}$
  - $T_{1/2} = 11.4 \text{ d}$
  - Decay energy of $^{223}\text{Ra}$ & daughters:
    - 95% $\alpha$-particles, 1% $\gamma$-rays
  - Daughters short-lived:
    - Seconds to minutes
      - $\alpha$-particle recoil unimportant
      - Migration of daughters negligible
Dosimetry

- **Mean Ds** *
  - Gut (LLI): 17 cGy / 50 kBq/kg
  - Red Marrow: 51 cGy / 50 kBq/kg
  - Bone: 420 cGy / 50 kBq/kg

- Ds **lower** to at-risk cells?

* Bayer Healthcare data: MIRD/OLINDA, 70-kg Standard Man

Sub-threshold doses for deterministic effects
Radiation Safety

• Low administered activities
  - $<<^{99m}Tc$, $^{18}$FDG activities:
    95 $\mu$Ci for 70-kg Standard Man

• Minimal radiation hazard
  - $<<^{99m}Tc$, $^{18}$FDG exposure rates
  - TI < Yellow II

• Disposal by decay-in-storage

• Outpatient Tx
  - Negligible hazard to staff, family members etc
Logistics

- Ready-to-inject solution
  - No preparation

- Stable, vialed drug
  - RaCl salt
  - Shelf-life: 28 days
  - Calibrated [A], 1,000 kBq/ml

- Weight-normalized, patient-specific dosing: 50 kBq/kg

\[
\text{Volume to inject (ml)} = \frac{\text{Body weight (kg)} \times 50 \text{ kBq/kg}}{\text{Decay factor} \times 1,000 \text{ kBq/ml}}
\]
Conclusion

$^{223}\text{Ra-Radium Chloride}$ is a safe, effective, and convenient treatment for skeletal metastases, delivering high biologically effective doses to malignant cells in bone with sparing of hematopoietic marrow and other normal tissues.

...Issues?

Issues

• 2° Malignancies?
• Calibration - End-user calibration
• Licensure
# Malignancies?

- Causal association between $\alpha$-emitters and human cancers

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Nuclide</th>
<th>Cancer Site(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radium dial painters</td>
<td>Radium-226</td>
<td>Bone</td>
</tr>
<tr>
<td>Thorotrast patients</td>
<td>Thorium-232</td>
<td>Liver, Leukemia</td>
</tr>
<tr>
<td>Ankylosing spondilytis patients</td>
<td>Radium-224</td>
<td>Bone, Leukemia</td>
</tr>
</tbody>
</table>

- Any $2^\circ$ malignancies (bone, leukemias) among $^{223}\text{Ra-RaCl}$ pts to date?
- Unlikely
  - Life expectancy of CRPC pts $\approx 1$ y
Calibration of Administered Activities

- **End-user calibration**
  - Is it necessary?
  - Can it be done accurately?
    (low administered & residual activities)

- **Dose calibrators do not have** $^{223}$Ra setting

- $^{223}$Ra
  - Secular equilibrium
  - Complex decay scheme

- **NIST-traceable standard**
Licensure

• Any special credentialing required to administer $^{223}$RaCl?

• §35.300 applies

• Credentialing options
  - §35.390, Category (3)
  - §35.390, Category (4)
  - §35.390, New Category for $\alpha$-emitters
  - §35.1000, “Other” - License amendment

• §35.57
  - AUs already satisfying 3-case requirement for Tx (§35.392 & 35.394) “grandfathered”
Abbreviations and Acronyms

• [A]: Activity concentration
• ACMUI: Advisory Committee on Medical Uses of Isotopes
• CRPC: Castrate-resistant prostate cancer
• D: Dose (radiation absorbed dose)
• FDG: Fluoro-deoxyglucose
• GI: Gastrointestinal
• LET: Linear Energy Transfer
• LLI: Lower large intestine
Abbreviations and Acronyms

• **MIRD**: Medical Internal Radionuclide Dosimetry (Committee)

• **OLINDA**: Organ-Level Internal Nuclide Dosimetry Algorithm

• **pt**: Patient

• **R**: Range

• **RBE**: Relative Biological Effectiveness

• **TI**: Transport Index

• **Tx**: Therapy