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

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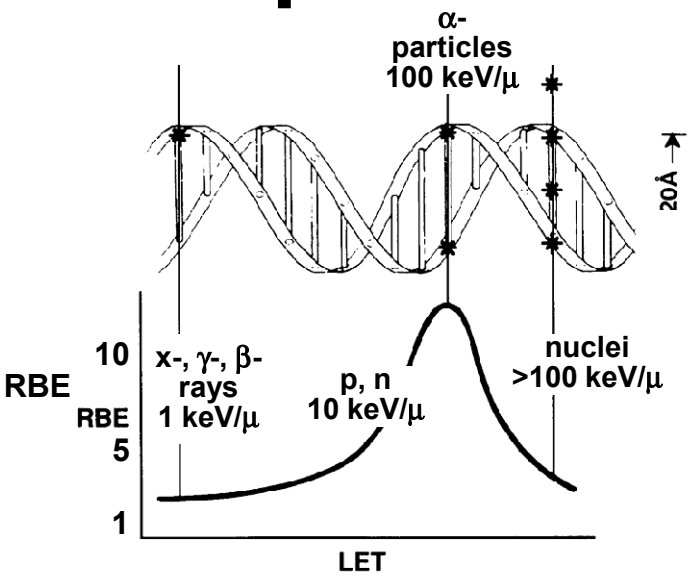
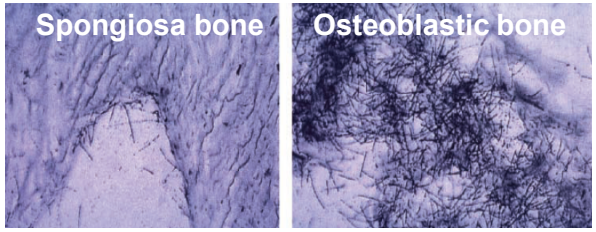
Radiobiology

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





Brulan OS et al. Clin Cancer Res 12: 6250s, 2006

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

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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**

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Physical Data

- **^{223}RaCl**
  - **$T_{1/2}$ = 11.4 d**
  - **Decay energy of ^{223}Ra & daughters: 95% α-particles, 1% γ-rays**
  - **Daughters short-lived: Seconds to minutes**
    - **α-particle recoil unimportant**
    - **migration of daughters negligible**

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Dosimetry

Sub-threshold doses for deterministic effects

- **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**

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Radiation Safety

- **Low administered activities**
  - **<< ^{99m}Tc, ^{18}FDG activities:**
    95 μCi 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**

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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**

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

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Conclusion

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

...Issues ?

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Issues

- **2°Malignancies?**
- **Calibration - End-user calibration**
- **Licensure**

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2°Malignancies?

- **Causal association between α-emitters and human cancers**

Cohort	Nuclide	Cancer Site(s)
Radium dial painters	Radium-226	Bone
Thorotrast patients	Thorium -232	Liver, Leukemia
Ankylosing spondilytis patients	Radium-224	Bone, Leukemia

- **Any 2°malignancies (bone, leukemias) among ^{223}Ra-RaCl pts to date?**
- **Unlikely**
  - **Life expectancy of CRPC pts ≈ 1 y**

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Calibration of Administered Activities

- **End-user calibration**
  - **Is it necessary?**
  - **Can it be done accurately? (low administered & residual activities)**
- **Dose calibrators do <u>not</u> have ^{223}Ra setting**
- **^{223}Ra**
  - **Secular equilibrium**
  - **Complex decay scheme**
- **NIST-traceable standard**

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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 α-emitters**
  - **§35.1000, "Other" - License amendment**

γ_s, β_s
Not "emissions-specific"

- **§35.57**
  - **AUs already satsfying 3-case requirement for Tx (§35.392 & 35.394) "grandfathered"**

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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

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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