



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

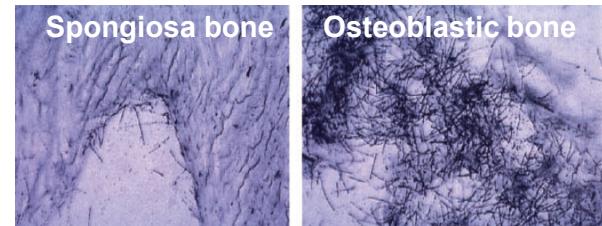
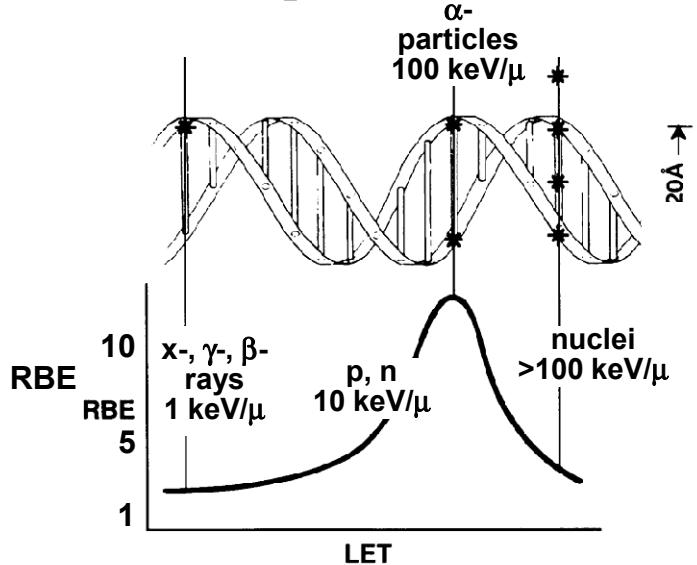
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Radiobiology

- **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

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}Ra & daughters:
95% α -particles, 1% γ -rays**
 - **Daughters short-lived:** }
Seconds to minutes }
 - α -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?**

*Sub-threshold doses
for deterministic effects*

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

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 \leq 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**



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

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
?

Issues

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

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 spondylitis 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

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 $^{223}\text{RaCl}$?
- §35.300 applies
- Credentialing options
 - §35.390, Category (3)
 - §35.390, Category (4)
 - §35.390, New Category for α -emitters ^{γ_s β_s}
Not "emissions-specific"
 - §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**