CURRENT STATUS AND POTENTIAL OF ALPHA-EMITTING RADIOPHARMACEUTICALS

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NO DISCLOSURES

Objectives

• Aware of the types of radionuclides with therapeutic potential.
• Familiar with the relative therapeutic properties of radionuclides.
• Aware of terminology used in radiopharmaceutical therapy, with particular reference to dosimetry and efficacy.
• Aware of the nature of alpha-particle radiopharmaceuticals currently in clinical trials/practice.
• Aware of challenges and potential, including regulatory issues, of alpha-particle radiopharmaceutical therapy.
SYSTEMIC RADIOTHERAPY

• The first targeted therapy was I-131 in thyroid disorders
• Principle: Accumulation in specific cells
  • of radioactivity
    • (I-131, Sr-89, Ra-223)
  • of ligands carrying radioactivity
    • (Sm-153 EDTMP, Y-90 Zevalin)

RADIOTHERAPY IN CANCER
Radionuclides with therapeutic potential

• $^{131}$I*#
  $T_{1/2}$ 8 days; $\beta^{-}_{\text{ave}}$ 191 KeV

• $^{90}$Y#
  $T_{1/2}$ 2.67 days; $\beta^{-}_{\text{ave}}$ 934 KeV

• $^{177}$Lu*
  $T_{1/2}$ 6.7 days; $\beta^{-}_{\text{ave}}$ 150 KeV

• $^{67}$Cu#
  $T_{1/2}$ 62 h; $\beta^{-}_{\text{ave}}$ 141 KeV

• $^{186}$Re*
  $T_{1/2}$ 3.78 days; $\beta^{-}_{\text{ave}}$ 362 KeV

• $^{188}$Re*
  $T_{1/2}$ 17 h; $\beta^{-}_{\text{ave}}$ 795 KeV

http://nucleardata.nuclear.lu.se/Database/nudat/
RADIOTHERAPY IN CANCER

Alpha-emitting Radionuclides

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>T-half</th>
<th>Energy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{211}$At*</td>
<td>7 hrs</td>
<td>7.5 MeV</td>
<td>Conjugation complex; Production fraught. Stable iodine block.</td>
</tr>
<tr>
<td>$^{213}$Bi*</td>
<td>46 mins</td>
<td>8.4 MeV</td>
<td>Chelation chemistry not universally applicable. DOTA most reliable and versatile chelator. Linkers not necessarily required.</td>
</tr>
<tr>
<td>$^{225}$Ac*</td>
<td>10 days</td>
<td>22+ MeV</td>
<td></td>
</tr>
<tr>
<td>$^{223}$Ra*</td>
<td>12 days</td>
<td>22+ MeV</td>
<td></td>
</tr>
<tr>
<td>$^{227}$Th*</td>
<td>19 days</td>
<td>27+ MeV</td>
<td></td>
</tr>
</tbody>
</table>

* All may be imaged, not high quality

http://nucleardata.nuclear.lu.se/Database/nudat/

Cytotoxic radionuclides

- Beta emitters
  - I-131
  - Y-90
  - Lu-177
    - Cu-67
    - Re-186; Re-188

- Deposition of low energy over variable lengths (0.5 – 3 mm)
Cytotoxic radionuclides

- Auger emitters
  - Deposition of high energy over VERY short path lengths (1-2 cell diameters).

- Alpha emitters
  - Bi-213
  - At-211
  - Ac-225
  - Ra-223
  - Deposition of high energy over short path lengths (10-50 cell diameters).

Therapy with alpha-, Auger- and beta-emitting nuclides

- Auger emission – one cell diameter – for cytoplasmic/intranuclear decay – high LET
- Alpha emission – 5-15 cell diameters – for small tumor clusters <200 μ – high LET
- Beta emission – deposition (function of energy) over several mm. – for established disease – low LET
Linear Energy Transfer (LET)

Clustered ionizations from low-energy electron
Single ionization

-- high probability of damage when alpha-particle hits DNA.

Delta-ray electron

RBE > 20


At-211 labeled antibodies


CRPC and bone metastases

Prostate cancer is the most bone tropic solid tumor

• Bone/soft tissue ratios are exceptionally high for metastatic prostate cancer

• More than 90% of metastatic prostate cancer (mCRPC) patients have osseous metastases

Limitations of β- emitters used for bone metastases

• Approved only for pain palliation
• Toxicity dose-limiting
  • May overlap with chemo-toxicity
• Hematopoietic toxicity
  • Thrombocytopenia
  • Usually reversible
  • Interval (>12 weeks) between therapies
• No effect on natural course of disease
  • When used as monotherapy
Alpha-particle Radiopharmaceutical therapy in castration-resistant prostate cancer

• Unique opportunity to use radiopharmaceutical therapy in CRPC to
  • EXTEND SURVIVAL
  • Palliate pain

• Safe agent with minimal toxicity
• Universal precautions ALONE sufficient

Ra-223: Preferential Uptake in Lesion Stroma

Note the short track length
Ra-223 Emissions

Ra-223 Main Branch

4 α particles  
(~28 MeV, ~95%)
2 β particles

Multiple X/γ particles allow imaging & PK

Ra-223 Imaging

200kBq/kg
13 MBq (0.36 mCi)
all energy windows combined
Shows very long retention in bone

EJNMMI. 2013; 40: 1384
Ra-223 Imaging

Safety: Dose rates to Public

Administered activities are low
50 kBq/kg (1.3 μCi/kg): (~ 3.5 MBq (95 μCi) for 70 kg patient)
Exposure rates to staff and public from patients undergoing treatment are very low.

<table>
<thead>
<tr>
<th>Time</th>
<th>Contact</th>
<th>30 cm</th>
<th>1 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>~0</td>
<td>0.52</td>
<td>0.086</td>
<td>0.012</td>
</tr>
<tr>
<td>24 h</td>
<td>0.80</td>
<td>0.14</td>
<td>0.019</td>
</tr>
<tr>
<td>48 h</td>
<td>0.27</td>
<td>0.016</td>
<td>0.012</td>
</tr>
</tbody>
</table>

(Dose-rate from patient with 444 MBq (12) mCi $^{18}$F-FDG ~ 40 μSv/h at 1m)

Dauer L et al, Health Physics 2014
MIRD Pamphlet No. 22 (Abridged): Radiobiology and Dosimetry of α-Particle Emitters for Targeted Radionuclide Therapy*

George Sgouros1, John C. Roeseke2, Michael R. McDevitt3, Sig Palms4, Barry J. Allen5, Darrell R. Fisher6, A. Bertrand Brill7, Hong Song1, Roger W. Howell8, and Gamal A. Akbani9

In collaboration with the SNM MIRD Committee: Wesley E. Bolch, A. Bertrand Brill, Darrell R. Fisher, Roger W. Howell, Roby F. Meredith, George Sgouros (Chair), Barry W. Wessels, and Pat B. Zattonico

1Department of Radiology and Radiological Sciences, Johns Hopkins University, Baltimore, Maryland; 2Department of Radiation Oncology, Loyola University Medical Center, Maywood, Illinois; 3Departments of Medicine and Radiology, Memorial Sloan-Kettering Cancer Center, New York, New York; 4Dosimetry and Medical Radiation Physics Section, International Atomic Energy Agency, Vienna, Austria; 5Centre for Experimental Radiation Oncology, St. George Cancer Centre, Kogarah, Australia; 6Radioisotopes Program, Pacific Northwest National Laboratory, Richland, Washington; 7Department of Radiology, Vanderbilt University, Nashville, Tennessee; 8Division of Radiation Research, Department of Radiology, New Jersey Medical School Cancer Center, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; and 9Department of Nuclear Engineering, Texas A&M University, College Station, Texas

J Nucl Med 2010

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**ALSYMPCA**

(ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design

**TREATMENT**

6 injections at 4-week intervals

- Radium-223 (50 kBq (1.35uCi/kg) + Best standard of care
- Placebo (saline) + Best standard of care

**PATIENTS**

Confirmed symptomatic CRPC
≥2 bone metastases
No known visceral metastases
Post-docetaxel or unfit for docetaxel

**STRATIFICATION**

Total ALP:
<220 U/L vs ≥220 U/L
Bisphosphonate use:
Yes vs No
Prior docetaxel:
Yes vs No

**RANDOMIZED**

2:1

N = 922

Planned follow-up 3 years
Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

Overall Survival & Bisphosphonate Use

Current

Ra223, n = 250
Median: 15.3 months
Placebo, n = 124
Median: 11.5 months

HR = 0.699
95% CI, 0.525-0.931
P = .01378

NO current

Ra223, n = 364
Median: 14.5 months
Placebo, n = 183
Median: 11.0 months

HR = 0.736
95% CI, 0.587-0.923
P = .00775


Nuclear Medicine aspects of Ra-223 therapy

• Safe, easy to administer
• Out-patient
• Therapy q4weeks x 6 (~6 months total)
  • Unless other therapy initiated for PoD
• Hematologic toxicity comparable to placebo
Logistics

• Verify measurable/evaluable disease
• Verify adequate hematologic parameters
  • ANC >1.5, Plt >100K, Hgb >10 recommended
• NO radiation safety directions/isolation
  • Plastic gloves adequate for shielding
• Imaging possible
  • Poor quality
    • Targeting demonstrable
    • Bowel significant

No deleterious effects precluding subsequent therapy

• Post-hoc analysis (Sartor et al) of 147 patients who received therapy after Ra-223 or placebo
  • Similar toxicity
  • Similar overall survival
**Licensing issues: 10CFR Part 35**

- Facility license amendment for Ra-223 (Z=88)
- 35.300 – Use of unsealed product for which a written directive is required
  - Physicians already authorized to parenterally administer therapeutic radiopharmaceuticals for medical use under § 35.396

http://pbadupws.nrc.gov/docs/ML1300/ML13008A149.pdf

**ALSYMPCA Conclusions**

In CRPC patients with bone metastases

- Radium-223 significantly prolongs
  - Overall Survival
    - $P$ value = .00185; HR = 0.695; 95% CI, 0.552-0.875
  - Time to first clinically relevant SSE
    - $P$ value = .00046; HR = 0.610; 95% CI, 0.461-0.807
- Radium-223 is very well tolerated
  - (Hematologic) Toxicity comparable to placebo
Conclusions

FDA & NRC – making Ra-223 easy
Rapid blood clearance
   Little or no urinary excretion
Rapid targeting to bone
Slow clearance via the gut – fecal excretion
Little or no redistribution from Ra-223 decay site
No requirement for written directive
Very low dose-rates to staff and public

Overall Conclusions

• Ra-223, a bone-targeting alpha emitter, has been demonstrated to prolong survival in CRPC
  • Therapy is safe, convenient, and out-patient
  • Side effects are reversible
  • Therapy is effective regardless of past/current therapy, and does not preclude future therapy

• Future directions include combination therapies
Ra-223 therapy in CRPC

- Opportunity for Nuclear Medicine physicians to rejuvenate radiopharmaceutical therapy
- Work closely with referring clinician to manage the patient over a 6-month period to assess
  - Toxicity
  - Performance status
  - Quality of life

Actinium-225
**HuM195 Blast Targeting Model**

*Antibody binds to all targets not only those in the marrow*

Time dependent labeled $^{213}$Bi-HuM195 activity distribution between spleen, liver and marrow

![Radiographic images](image)

Bi-213 gammas (~440 KeV)

Day 0

Day 0 pm

Day 1

Day 1 pm

Clin Cancer Res. 2010; 16: 5303

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**Actimab-A Phase 1 – Safety**

*In advanced age patients with high risk factors Actimab-A was safe with low mortality and few side effects*

- Patients treated at 4 dose levels
- No early mortality at 28 days from treatment start
- 56 days early mortality 11% (2 of 18 patients)
- MTD not reached
- **2 DLTs**, one each at 1 μCi/kg/fraction (1/6) and 2 μCi/kg/fraction dose level (1/6)
  - Patient treated at 1 μCi/kg/fraction had late recovery and achieved CR and long term survival (3 years plus), patient treated at 2 μCi/kg/fraction too early to tell
  - 1 DLT was G4 thrombocytopenia and 1 DLT G4 leukopenia
- **No extramedullary DLTs**
- As expected in this group of older patients with high risk factors, all but one patient experienced SAEs
  - Most SAEs were expected consequences of AML: infections and cytopenias
  - SAEs other than infection and cytopenia related were observed in one patient each across dose levels (no discernible trend)
**Actimab-A Phase 1 Efficacy**

*Actimab-A showed significant efficacy in patients with very limited treatment options*

- 18 patients (median age, 77 years; range, 68-87 years) completed therapy
  - 14 (78%) 75 and older
  - 5 (28%) 80 and older
  - 12 (67%) had prior MDS
  - 9 (75%) had prior therapy (8 HMA, 1 allo-SCT)
  - 11 (67%) had intermediate-risk and 7 (33%) had unfavorable cytogenetics
- 4 out of 5 responses were seen at two highest dose levels (4/9 treated patients)

<table>
<thead>
<tr>
<th>Response</th>
<th>Dose Level (µCi/kg/fraction)</th>
<th>Total (n=18)</th>
<th>Total 1+ (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 (n=3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/CRp/CRi</td>
<td>0</td>
<td>1 (17%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td></td>
<td>1 (n=6)</td>
<td>2 (67%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td></td>
<td>1.5 (n=3)</td>
<td>2 (33%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (n=6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Impact of PB Burden – Phase 1 Trial

*Improved dose response observed in patients with low peripheral blast burden*

**Fractionated dose & LDAC**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>µCi/kg</th>
<th>Pts #</th>
<th>CRc</th>
<th>DLTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 x 0.5</td>
<td>3</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2 x 1</td>
<td>6</td>
<td>17%</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>2 x 1.5</td>
<td>3</td>
<td>67%</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2 x 2</td>
<td>6</td>
<td>33%</td>
<td>1</td>
</tr>
</tbody>
</table>

**Fractionated dose & LDAC – low PB only**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>µCi/kg</th>
<th>Pts #</th>
<th>CRc</th>
<th>DLTs</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>2 x 0.5</td>
<td>1</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2 x 1</td>
<td>3</td>
<td>33%</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>2 x 1.5</td>
<td>3</td>
<td>67%</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2 x 2</td>
<td>4</td>
<td>50%</td>
<td>1</td>
</tr>
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</table>
**225**Ac-PSMA-617 in CRPC


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Alpha-radiopharmaceutical therapy

• High linear energy transfer (LET) produces irreparable DNA strand breaks
• Short path length minimizes off-target radiation
• Potential therapeutic radioactivity window without dose-limiting toxicity
• Minimal radiation safety precautions

• Off-target binding
• Daughter nuclides
• Dosimetry estimates
• Radiochemical features

Conclusions

• Ra-223 prolongs survival in mCRPC
• Bi-213 anti-CD33 mAb has shown significant responses in CML
  • Ac-225 Actimab-A® Phase 2 ongoing
• Ac-225 anti-PSMA small molecules have shown dramatic responses in mCRPC

• EFFICACY WITH MANAGEABLE TOXICITY
• CONVENIENT AND SAFE ADMINISTRATION