An Overview of Radiopharmaceutical Therapy (RPT): Past, Present, and (Primarily) Future

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Radiopharmaceutical Therapy (RPT)

• Definition: Use of a systemically or locally delivered radiopharmaceutical that either binds preferentially to or accumulates by physiological mechanisms in the intended “target”.¹

• Is a targeted approach without use of an external beam.
Historical Perspective

- RPT is certainly not new. [e.g., P-32 for prostate cancer as early as 1936\(^2\); or radioiodine in the 1940’s for thyroid cancer\(^3\)]
- Other Examples:
  - Au-198 or P-32 as liquid colloid, instilled into pleural or abdominal cavity for treatment of ascites or pleural effusions
  - P-32 administered orally to treat polycythemia vera.
  - P-32 delivered locally to treat nasopharyngeoma.
  - Y-90 as liquid colloid to treat rheumatoid conditions
More recently...

- **Metastron** ($^{89}\text{Sr}$-chloride) for bone pain from metastatic cancer lesions. FDA approval 1993.
- **Quadramet** ($^{153}\text{Sm}$ lexidronam pentasodium) for bone pain from metastatic cancer lesions. FDA approval 1997.
- **$^{131}\text{I}$-MIBG** ($^{131}\text{I}$-metaiodobenzylguanidine). FDA approved for pheochromocytoma in 1994. [Approved for other uses subsequently.]
- **$^{90}\text{Y}$ microspheres** (SirSpheres/Theraspheres) for treatment of liver tumors. FDA approval of Sirspheres March 2002. Approval of Theraspheres 2021.
- **Xofigo** ($^{223}\text{Ra}$-dichloride) for the treatment of metastatic castration resistant prostate cancer. FDA approval May 2013.
- **Lutathera** ($^{177}\text{Lu}$-dotatate) for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs). FDA approval January 2018.
What’s ahead?

Let’s defer that until later in the presentation
RPT Agents - General Categories

- Elemental and unconjugated or chelated radionuclides
- Small molecule
- Peptides
- Antibodies
- Nanoconstructs (including liposomes)
- Microspheres
Elemental, unconjugated, and/or chelated

- Elemental radionuclide itself (with or without another non-radioactive drug)
- Salts (e.g., iodides, chlorides, etc.)
- Chelated forms
Examples (elemental, etc.)

- P-32 (with or without simultaneous administration of androgens). Non-specific targeting without androgens. Androgens improved uptake in metastatic bone lesions.\(^2\)
- NaI-131. Iodine selectively taken up by differentiated follicular thyroid cells (normal physiological process). No uptake by cancer cells of non-follicular origin or by cancer cells that have reverted to non-differentiated forms.\(^1\)
- Y-90, P-32, Rh-186, Erbium-169 (in Europe only), in colloidal forms (e.g., P-32 chromic phosphate). Direct intra-articular injection for synovitis.\(^4\)
- Sm-153. As \(^{153}\)SmCl\(_3\), chelated with phosphate ligands [e.g., “Quadramet”, bound to 4 phosphate ligands and 2 amines], taken up by growing bone in metastatic bone lesions.\(^1\)
- Ra-223. As \(^{223}\)RaCl\(_2\) (“Xofigo”). Calcium analog taken up by growing bone in metastatic bone lesions.\(^1\)
“Quadramet” (chelate example)

(image from Quadramet package insert)

The structural formula of samarium lexidronam pentasodium is:

The ionic formula is $^{153}\text{Sm}^{3+} [\text{CH}_2\text{N} (\text{CH}_2\text{PO}_3\text{O}^-)_2]_2$ and the ionic formula weight is 581.1 daltons (pentasodium form, 696).
Small molecule

- Radionuclides bound to “targeting vectors”, for example:
  - Bound to analogs of normal human molecules of physiologic importance (e.g., neurotransmitters)
  - Bound to molecules that will bind to specific receptors found on the cancer cells to be targeted (e.g., PSMA and folate receptors)
  - Bound to phospholipid ether analogs - does not target a specific receptor but targets the “overabundance of lipid rafts found on cancer cell membranes”.
- Other(?)
Small molecule examples

• $[^{131}\text{I}]\text{mIBG}$ ($^{131}\text{I}$-meta-iodobenzylguanidine), an analog of the neurotransmitter for treatment of neuroblastomas

• Various PSMA or folate receptor agents (e.g. $^{177}\text{Lu}$-labelled PSMA-617; $^{227}\text{Th}$-labelled PSMA-TTC) in clinical trials

• Labelled phospholipid ether analogs targeting cancer cell-specific lipid raft microdomains (e.g. $^{131}\text{I}$-labelled CLR 131; $^{131}\text{I}$-labelled CLR1404) in clinical trials
Novartis announced today that the US Food and Drug Administration (FDA) has granted Breakthrough Therapy designation (BTD) to $^{177}$Lu-PSMA-617, an investigational radioligand therapy for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Breakthrough Therapy designation is granted to medicines being evaluated for serious conditions where early clinical evidence indicates the potential for substantial improvement over available therapy.”
Peptides\textsuperscript{1}

- Essentially, targeting various receptors as with the “small molecules” category, but the targeting agents are larger peptides
- Frequent receptor targets include:
  - Somatostatin receptors
  - Bombesin receptors
Peptide examples

- $^{177}$Lu-DOTATATE (“Lutathera”) for treatment of neuroendocrine tumors. FDA approved.
- $^{177}$Lu-labelled NeoBOMB1 (for gastroenteropancreatic cancer). In clinical trials.
- $^{177}$Lu-labelled RM2 (for gastroenteropancreatic cancer). In preclinical development.
- $^{90}$Y-octreotide ($^{90}$Y-DOTA-Tyr$^3$-octreotide) for neuroendocrine tumors. In clinical trials.
Antibodies

- Labelled antibodies, target multiple receptors
- Antibodies mostly in the “IgG” class have been studied for RPT
- Specific monoclonal antibodies used
- To date, mostly studied for hematological and lymphoid cancers
Target antigens that have been used in antibody-based radiopharmaceutical therapy. From: Radiopharmaceutical therapy in cancer: clinical advances and challenges

Antibodies to a variety of tumour-associated targets may be raised, including leukaemia-associated and lymphoma-associated targets (for example, CD20, CD45 and CD33), targets expressed on solid-tumour cancer cells (for example, carcinoembryonic antigen (CEA), prostate-specific membrane antigen (PSMA) and GD2) and targets expressed on their supporting microenvironment (for example, fibroblast activation protein-α (FAPα)). AML, acute myelogenous leukaemia; APC, antigen-presenting cell; BAFF-R, B cell-activating factor receptor; CAIX, carbonic anhydrase 9; DR, death receptor; slg, secretory immunoglobulins. Adapted from ref. 305, Springer Nature Limited.
Antibody-based (examples) \(^1\)

- \(^{225}\)Ac-labelled aCD38 (for multiple myeloma). In clinical trials.
- \(^{225}\)Ac-labelled aCD33 (for leukemia; myelodysplastic syndrome). In clinical trials.
- \(^{212}\)Pb-labelled aCD37 (for leukemia/lymphoma). In preclinical development.
- \(^{227}\)Th-labelled aCD22-TTC (for lymphoma). In clinical trials.
Nanoconstructs\textsuperscript{1,5}

- Nanomaterials may be:
  - Inorganic
  - Polymeric
  - Carbon-based
  - Liposomes

- Nanomaterials may radiolabeled by:
  - Chelation
  - Entrapment
  - Sorption
  - Covalent bonding

- One advantage of nanoconstructs is that each nanoparticle may incorporate multiple radioactive atoms
*Figure 2. Incorporation of therapeutic radionuclides into the nanocarrier by (a) chelation, (b) entrapment, (c) sorption, and (d) covalent bonding.

Many Possible Radioisotopes

<table>
<thead>
<tr>
<th>Beta emitters (e.g.)</th>
<th>Alpha emitters (e.g.)</th>
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<tbody>
<tr>
<td>I-131</td>
<td>At-211</td>
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<tr>
<td>Cu-67</td>
<td>Bi-212</td>
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<tr>
<td>Y-90</td>
<td>Bi-213</td>
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<td>Ho-166</td>
<td>Ra-223</td>
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<td>Lu-177</td>
<td>Ac-225</td>
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<td>Re-186</td>
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<td>Re-188</td>
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<td>Au-198</td>
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Microspheres

- Radiolabeled glass or resin spheres (~20-60 micron diameter)
- Differentiation from nanoconstructs is primarily a matter of size
Microsphere examples

- $^{90}$Y-SIR-Spheres. Resin spheres, 20-60 micron diameter, for hepatic tumors. FDA approved.
- $^{90}$Y-TheraSpheres. Glass spheres, 20-30 micron diameter, for hepatic tumors. FDA approved.
- $^{32}$P-labelled glass microspheres.\(^1\) For radioembolization (under study).
- $^{166}$Ho-labeled biodegradable poly(L-lactic acid) microspheres.\(^1,6\) In clinical trials
Uncertain categorization

- Radiolabeled iodized oils\(^1\) delivered trans-arterially for hepatocellular malignancies. [Clinical trials.]
  - \(^{131}\)I-labelled iodized oil ("Lipiodol")
  - \(^{188}\)Re-labelled iodized oil
So what can be said about the future?

• Many new RPT agents in clinical trials or pre-clinical development will be seen (or are already being seen) at many healthcare and biomedical research facilities. [Reference #1 provides a table listing examples of 31 agents already commercially available or in various stages of development.]

• Many of these agents will ultimately gain FDA approval and become commercially available, so utilization will spread beyond those facilities where clinical research and human trials are performed.

• Some already commercially available agents may find new uses (i.e. different malignancies to treat) so numbers of procedures will go up).

• Some already commercially available agents may become paired with other non-radioactive treatments (improving efficacy), again with the potential for higher workloads.
Recent news story.....

So the likely scenarios are that....

- Historically “familiar” isotopes will continue to be used in familiar forms (RPT agents), for familiar therapy targets (conditions treated)
- Familiar isotopes, in familiar forms, may find new uses (or increased uses)
- Familiar isotopes, in new RPT agents, will be used for new and/or familiar targets
- Unfamiliar (rarely used to-date) isotopes will be used with both familiar and new agents, for new and/or familiar targets
For the **Medical Health Physicist (and Regulator)**....

- Each new use or RPT agent will have to be evaluated, and related issues addressed, based on:
  - Radiological characteristics of the radionuclide
  - Physical characteristics of the radiolabeled agent
  - Chemical characteristics of the radiolabeled agent
  - Biological/physiological characteristics of the radiolabeled agent
  - Biological/physiological characteristics of the specific patient population (e.g., incontinence?)
  - Caregiver needs post-therapy

- Considerations:
  - Radiation levels
  - Shielding
  - Contamination control (including patient skin)
  - Patient and caregiver instructions
BUT REALIZE THAT.....

• Even though there will be use of radionuclides that have not been commonly used, the medical community already has decades of experience with energetic beta and/or gamma emitters (and now years of experience alpha-emitting radiopharmaceuticals).
• The “unfamiliar” radioisotopes do NOT pose any unique or unusual radiological hazards or related challenges (e.g., detection) compared to those that we already deal with.
• There will be nothing new about the modes of administration (i.e., “parenteral”) used to deliver these RPT agents to patients.
• With the exception of “microspheres”, all of the categories of RPT agents discussed in this presentation meet the criteria as is 10 CFR35.300 (i.e., no new regulations are needed - only the awareness of how to apply appropriate, standard radiation protection procedures are necessary).
Some of those “Unfamiliar” Radioisotopes
Copper $\text{-}^{67}$ ($\text{Cu-}^{67}$)

- Primary emission: beta ($0.58 \text{ MeV}_{\text{max}}$)
- Significant other emissions: Zn x-rays including $0.184 \text{ MeV}$, 40%
- Half-life: 2.60 days
- Progeny: Zn-67
Holmium-166 (Ho-166)

- Primary emission: beta (1.85 MeV$_{\text{max}}$)
- Significant other emissions: γ’s (0.08 MeV, 5.4%; some others up to 1.66 MeV but low yield)
- Half-life: 1.12 days
- Progeny: Er-166
Rhenium-186 (Re-186)

- Primary emission: beta ($1.07 \text{ MeV}_{\text{max}}$)
- Significant other emissions: γ’s (11%, highest 0.137 MeV)
- Half-life: 3.72 days
- Progeny: Os-186
Rhenium-188 (Re-188)

- Primary emission: beta \((2.12 \text{ MeV}_{\text{max}})\)
- Significant other emissions: \(\gamma\)'s (8.3%, mostly 0.155 MeV)
- Half-life: 17 hours
- Progeny: Os-188
Gold-198 (Au-198)

- Primary emission: beta ($0.96 \text{ MeV}_{\text{max}}$)
- Significant other emissions: $\gamma$’s (primarily $0.412 \text{ MeV}$, 95%)
- Half-life: 2.70 days
- Progeny: Hg-198
Astatine-211 (At-211)

- Primary emission: alpha (to Bi-207); beta (to Po-211)
- Significant other emissions: none
- Half-life: 7.2 hours
- Progeny: Bi-207 or Po-211 (Po-211 decays by alpha to Pb-207 with a 0.516 sec half-life)
Lead 212 (Pb-212)

- Primary emission: beta ($0.58 \text{ MeV}_{\text{max}}$)
- Significant other emission: $\gamma$ ($0.24 \text{ MeV}$, 47%)
- Half-life: 10.6 hours
- Progeny: Bi-212 (alphas [35%], $T_{1/2} = 1.0 \text{ hour}$; associated beta and multiple gammas up to 1.62 MeV, $<14\%$ total)
Actinium-225 (Ac-225)

- Primary emissions: alphas
- Significant other emissions: Fr x-rays; various daughter radiations
- Half-life: 10.0 days
- Progeny: Decay chain from Fr-221 ending at Pb-209 (includes 4 alpha emissions after Ac-225)
Thorium-227 (Th-227)

- Primary emission: alphas
- Significant other emissions: $\gamma$’s - 0.05 MeV (8%). 0.237 MeV (15%), 0.31 MeV (8%)
- Half-life: 18.2 days
- Progeny: Ra-223
References

“Stop! Who would cross the Bridge of Death must answer me these questions three, ere the other side he see.”