Radionuclide Therapy: History, Present and Future Promise

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History Symposium 8/02/2017

History of Radionuclide (RN) Therapy

• Disclosures: None

History of RN Therapy

• Learning Objectives:
  1. Discuss the physiological basis and use of I-131 for treatment of hyperthyroidism and for papillary/follicular thyroid cancer.
  2. Discuss the use of somatostatin receptor-targeted therapy for neuroendocrine tumors.
  3. Discuss how beta and alpha emitters may be used, possibly in various combinations.
History of RN Therapy

• Learning Objectives that are more appropriate:
  • Be able to discuss the dosimetry involved in determining optimal I-131 therapy for Graves’ Disease.
  • Be able to discuss types of emissions, maximum energy and maximum range in tissue of various therapeutic radionuclides.

History of RN Therapy

• The first radionuclide treatment was of P-32 sodium phosphate by John Lawrence in 1936 for leukemia, and shortly thereafter by Hamilton in 1936 for treatment of polycythemia rubra vera.

History of RN Therapy

• I-131
  • Saul Hertz, M.D. first used I-131 (mixed with I-130) in 1941 to treat a patient with Graves’ Disease.
  • 1942 – presentation of results in first 10 pts
  • He initially treated a series of 29 patients. The results were published in a 5-year follow up in JAMA in 1946. 20 of 29 were cured.
History of RN Therapy

- I-131 is the first theranostic agent.
- Saul Hertz –
  - First use of radioiodine
  - First radioiodine studies of metabolism
  - First radioiodine treatment of hyperthyroidism - 1941
  - First radioiodine treatment of thyroid cancer - 1942

History of RN Therapy

- 1951 – 1952 William Beierwaltes
  - First successful radioimmunotherapy for cancer – in a patient with metastatic melanoma.
  - 27 mCi of I-131 labeled antibodies
  - Lesions disappeared and no recurrence for 9 years, when patient died from a car accident (autopsy revealed no malignancy).

History of RN Therapy

- Giants in Development of RN therapy
  - Paul Ehrlich – idea of the “magic bullet”
  - Saul Hertz – Father of radioiodine therapy
  - William Beierwaltes – radionuclide therapy of endocrine diseases, especially thyroid
  - Steve Larson – first Saul Hertz Award recipient at the 2016 SNMMI annual meeting
History of RN Therapy

• P-32 chromic phosphate for ovarian cancer, malignant ascites.

• 1980’s: I-131 metaiodobenzyl guanidine (MIBG) was introduced for treatment of neuroendocrine tumors
• Somatostatin receptor-targeted therapy introduced to treat various solid tumors
• Introduction of radiolabeled antibodies to treat solid tumors

History of RN Therapy

• 1980s: Bone pain palliation introduced.
  • Initially, P-32 sodium phosphate (also used for myeloproliferative disease) – No longer used due to possible side effects of pancytopenia and leukemia
  • Strontium-89 (Sr-89) chloride, 4 mCi given IV
  • Samarium-153 (Sm-153) EDTMP, 1.0 mCi/kg, given IV
Bone pain palliation

History of RN Therapy

• 1980s:
  • I-131 lipiodol – hepatocellular carcinoma (hepatoma)

History of RN Therapy

• 1983
  • Localization of I-131 p97-specific fragments in human melanoma as a basis for radiotherapy
History of RN Therapy

- Early 1980’s I-131 meta-iodobenzyl guanidine (I-131 MIBG) - invented by William Beierwaltes
- For neural crest tumors, including neuroblastoma, malignant pheochromocytoma, paraganglioma, medullary thyroid carcinoma and carcinoid tumors
- 1999 – objective response (>50% tumor volume reduction) in approx. 50% of pts with neuroblastoma, pheochromocytoma and paraganglioma
- 2004 – Proven value in neuroblastoma, has a place in management of malignant pheochromocytoma

History of RN Therapy

- 1994 – First Peptide Receptor Radionuclide Therapy (PRRT) – In-111 octreotide – using Auger electrons (mean range <1 um)
- Neuroendocrine tumors – gastrinomas and other gastroenteropancreatic neoplasms, malignant carcinoid, pheochromocytoma and paraganglioma, Merkel cell carcinoma (a rare undifferentiated small cell carcinoma of the skin), and others

History of RN Therapy

- 1994 – First In-111 octreotide PRRT
- 1996 – First Yttrium-90 (Y-90) octreotide PRRT
- 1997 – First Y-90 DOTATOC PRRT
- 2000 – First Lu-177 octreotate PRRT
- Target - a somatostatin receptor on the cell surface of tumor cells. These therapies take advantage of the bystander effect.
History of RN Therapy

• Two agents (radiolabeled antibodies) were introduced to treat CD20 positive non-Hodgkin’s lymphoma:

• 2002: Y-90 Ibritumomab Tiuxetan (Zevalin)
• 2003: I-131 tositumomab (Bexxar)

History of RN Therapy

• A few benign conditions:
• First and foremost: I-131 therapy of hyperthyroidism (Graves’ Disease, solitary autonomous nodule, toxic multinodular goiter)
• Radiation synovectomy, mainly for inflammatory (but non-infectious) processes, also for persistent effusion after knee prosthesis and for Baker’s cyst

Recent/Current List of Therapy

Radionuclides

<table>
<thead>
<tr>
<th></th>
<th>T1/2</th>
<th>Emission</th>
<th>Max E (keV)</th>
<th>Max range (mm)</th>
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<tbody>
<tr>
<td>RN</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>I-131</td>
<td>8 d</td>
<td>beta</td>
<td>610</td>
<td>2</td>
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<tr>
<td>Y-90</td>
<td>64 hr</td>
<td>beta</td>
<td>2280</td>
<td>12</td>
</tr>
<tr>
<td>Lu-177</td>
<td>6.7 d</td>
<td>beta</td>
<td>496</td>
<td>2</td>
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<tr>
<td>Cu-67</td>
<td>62 hr</td>
<td>beta</td>
<td>577</td>
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<tr>
<td>Re-186</td>
<td>91 hr</td>
<td>beta</td>
<td>1080</td>
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<td>Re-188</td>
<td>17 hr</td>
<td>beta</td>
<td>2120</td>
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<tr>
<td>In-111</td>
<td>2.8 d</td>
<td>beta (auger)</td>
<td>19</td>
<td>&lt;1</td>
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<td>Sr-89</td>
<td>50.57 d</td>
<td>beta</td>
<td>1463</td>
<td>8</td>
</tr>
<tr>
<td>Sm-153</td>
<td>46.3 hr</td>
<td>beta</td>
<td>805</td>
<td>3.0</td>
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**Recent/Current List of Therapy Radionuclides**

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>T1/2</th>
<th>Emission</th>
<th>Max E (keV)</th>
<th>Max range (mm)</th>
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<tbody>
<tr>
<td>Ra-223</td>
<td>11.4 d</td>
<td>alpha</td>
<td>7500</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Bi-212</td>
<td>1 hr</td>
<td>alpha</td>
<td>8780</td>
<td>0.09</td>
</tr>
<tr>
<td>Bi-213</td>
<td>0.77 hr</td>
<td>alpha</td>
<td>&gt;6000</td>
<td>&lt;0.1</td>
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<tr>
<td>At-211</td>
<td>7.2 hr</td>
<td>alpha</td>
<td>7450</td>
<td>0.08</td>
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<tr>
<td>Ac-225</td>
<td>10 d</td>
<td>alpha(s)-4</td>
<td>5790(8380)</td>
<td>0.01</td>
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<tr>
<td></td>
<td></td>
<td>beta(s)-3</td>
<td>1600</td>
<td>3</td>
</tr>
<tr>
<td>Tb-149</td>
<td>4.1 hr</td>
<td>alpha</td>
<td>3970</td>
<td>0.028</td>
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**Present**

- I-131 sodium iodide – hyperthyroidism and papillary/follicular thyroid cancer
- Somatostatin receptor targeted therapy (also known as Peptide Receptor Radionuclide Therapy (PRRT)) – for neuroendocrine tumors (NETs)
- I-131 MIBG for neural crest tumors, mainly neuroblastoma and malignant pheochromocytoma

**Present**

- Radioimmunotherapy of lymphoma – using Y-90 ibritumomab tiuxetan targeting the CD20 receptor on the cell surface of non-Hodgkin’s lymphoma
- Treatment of hepatic metastases (and also hepatocellular carcinoma) with Y-90 microspheres (glass beads or resin beads) by hepatic intra-arterial injection
Present

• Radium-223 dichloride – approved in 2013 for patients with castrate-resistant metastatic prostate carcinoma
• RN therapy for bone pain palliation, mainly Sm-153 EDTMP

Present

• The following are currently being used in Germany:
• Y-90 DOTATATE
• Y-90 DOTATOC
• Y-90 DOTANOC

Present

• Lu-177 DOTATATE for treatment of neuroendocrine tumors is now in clinical trials
• Lu-177 DOTATATE – midgut neuroendocrine tumors - NETTER-1 Trial
Present

- I-131:
  - Iodine is selectively taken up by the thyroid gland and incorporated into thyroid hormone
  - Chemically, stable iodine (I-127) and I-131 (and other I isotopes) are identical
  - I-131 is a beta-emitter and gamma-emitter (364 keV)
  - T ½ = 8 days

I-131 Sodium Iodide

- I-131 therapy for hyperthyroidism (toxic adenoma, multinodular goiter, and especially Graves’ Disease) is effective, safe and inexpensive.
- I-131 is administered orally (by capsule or liquid form), and is rapidly and completely absorbed.
- I-131 is quickly concentrated, oxidized, and organified by follicular cells of the thyroid.
- Peak uptake generally occurs at approx. 24 hours.

I-131 Sodium Iodide

- Ionizing effects of the beta emissions, which have a path length of 1-2 mm, destroy follicular cells, not only those cells that take up the I-131, but also adjacent follicular cells are irradiated, since the cell diameter is less than the path length of the beta emissions.
- An example of the bystander effect.
I-131 Sodium Iodide - Dosimetry

- For thyrotoxicosis, 50 – 150 Gy (5,000 – 15,000 rad) generally will reduce hormone secretion to normal or below normal levels.
- For many years, 80 uCi/g (7,000 rad/g) was considered ideal for treatment of Graves’ Disease.
- Currently, experts use 120-140 uCi/g.

I-131 Therapy for Graves’ Disease

- My preferred method:
- Delivered Radiation Dose Method

  \[ \text{Dosage (uCi)} = \frac{\text{cGy} \times \text{Tp} \times \text{est. gland weight (g)}}{\text{g-cGy/uCi I-131} \times \text{Teff} \times \text{Max Uptake}} \]

  Ref: Carol Marcus, Ph.D., M.D. UCLA

I-131 Therapy Graves’ Disease

- Delivered Radiation Dose Method - Example

  \[ \text{Dosage (uCi)} = \frac{12,000 \times 8d \times 60 \text{ g}}{120 \times 4d \times 0.6 \text{ (fractional = 60%)} \times 1,000} = 20 \text{ mCi} \]

  Ref: Carol Marcus, Ph.D., M.D. UCLA
I-131 Therapy for Thyroid Cancer

- Since papillary and follicular cell carcinomas function like normal thyroid, although less efficiently, they can be treated with I-131.
- Initial therapy is often 100 – 150 mCi.
- Remnant ablation can be achieved by 300 Gy (30,000 rad).

- Keep dose to bone marrow below 200 cGy (200 rad).
- In patients with miliary lung metastases, keep uptake by the lungs to less than 80 uCi (to avoid pulmonary fibrosis, a potentially fatal complication). Beierwaltes never observed lung uptake >40%; therefore, never treat with more than 200 mCi, and pulmonary fibrosis can be avoided.

- High level of controversy regarding:
  - Optimal prescribed activity - empiric fixed-dose or not
  - Adjuvant therapy
  - Treatment of recurrence
  - Metastatic disease
  - Quantitative tumor and blood dosimetry
Present/Future

• Lu-177 BPAMD therapy – endoradiotherapy of bone metastases
• Lu-177 CXCR4 and Y-90 CXCR4 - for multiple myeloma (theranostic agents with Ga-68 CXCR4)
• Lu-177 PSMA – RN therapy of metastatic castration-resistant prostate cancer

Present/Future

Courtesy of: Johannes Czernin, MD

Present/Future

Evidence for Renaissance II: Theranostics
Combination of therapeutic & diagnostic

Present/Future

Iodine-124 PET-CT Scans Obtained before and after Selumetinib Treatment in Selected Patients with Positive Responses

Courtesy of: Richard Baum, MD
Present/Future

Phase 3 Clinical trial: Radiolabeled antibody with I-131 for therapy of acute myeloid leukemia

Ref: David Gould, MD

Present/Future

Ref: David Gould, MD

Present/Future

Curing the incurable!

Courtesy of: Richard Baum, MD

Present/Future

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Target</th>
<th>Indication</th>
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<tbody>
<tr>
<td>^m</td>
<td>Functin (human)</td>
<td>LAT</td>
</tr>
<tr>
<td>^m</td>
<td>Chains</td>
<td>Chl</td>
</tr>
<tr>
<td>^m</td>
<td>DOTATATE (histidine)</td>
<td>SID</td>
</tr>
<tr>
<td>^m</td>
<td>Prostate (neutrophil)</td>
<td>$\gamma$-myloid</td>
</tr>
<tr>
<td>^m</td>
<td>Prostate (lymphoid)</td>
<td>$\gamma$-myloid</td>
</tr>
<tr>
<td>Radiolabeled (DOTEREG)</td>
<td>prostatic DAT</td>
<td>Movement O</td>
</tr>
</tbody>
</table>

Therapeutic: Prostate (neutrophil) bone turnover bone mat

Diagnostic Moldele Soon

- ^mPSMA
- L~P~F~D~O~F~A
- ^mPSMA/125I PSMA Prostate CA

Therapeutic: Moldele Soon

- ^m|DOTATATE
- ^m|DOTATATE/125I PSMA Prostate CA

Other therapeutic: Prostate, CXCR4, Neurotensin, FOLATE receptors: All approaches

Courtesy of Johannes Czernin, MD
Present/Future of RN Therapy

• Tumor heterogeneity is a key factor limiting response to targeted therapy.
• Personalized (precision) medicine depends on biomarkers for selecting patients and directing radionuclide therapy.

Ref: modified from James Thrall, MD

Future

• New targets, new ligands, improved peptides
• New radionuclides for imaging and therapy, including new alpha-emitters (possibly Ac-225, Bi-213, Tb-149)
• New combinations of RN therapy with other treatment modalities, especially immune modulation

Ref: Richard Baum, MD

Future

• RN therapy may include various combinations of alpha and beta emitters, to take advantage of different path lengths and energy levels, in combination with immune modulation and possibly also chemotherapy.
• However, RN therapy can take advantage of the bystander effect, which is not possible with chemotherapy.
I predict that future developments in cancer therapy will include specifically targeted (precision) RN therapy, with targeting of various enzymatic pathways, and cell-surface receptors, including clonal variations. These RN therapies will also rely on precise dosimetry, probably including intralesional dosimetry. These RN therapies may include combinations of alpha and beta-emitters, which may provide more comprehensive therapy, and lead to less morbidity and much improved outcomes.