Novel Radionuclide Therapies in Oncology: Promising Area in the Field of Nuclear Medicine

Erik Mittra, MD, PhD
Clinical Assistant Professor
Radiology / Nuclear Medicine
Objectives / Outline

1. Understand the basic principles of targeted radionuclide therapy.

2. Identify the currently available radionuclide therapies for treatment of cancer.

3. Discuss peptide receptor radionuclide therapy (PRRT) in neuroendocrine cancers

4. Understand alpha emitter therapy for prostate cancer metastases.
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Targeted Radionuclide Therapy
Targeted Radionuclide Therapy → Treatment of benign or malignant lesions
Targeted Radionuclide → Use of radiation to destroy lesions

Therapy → Treatment of benign or malignant lesions
Targeted → Delivery of radiation to specific tissue

Radionuclide → Use of radiation to destroy lesions

Therapy → Treatment of benign or malignant lesions
Targeted Radionuclide Therapy

Katie Walker, Lawrence Livermore National Lab
Choice of Carrier

Choice of Radionuclide
## Choice of Radionuclide

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>$T_{1/2}$</th>
<th>emission</th>
<th>mean path length</th>
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<tr>
<td>I-125</td>
<td>60.0d</td>
<td>auger</td>
<td>10nm</td>
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<tr>
<td>At-211</td>
<td>7.2h</td>
<td>alpha</td>
<td>65nm</td>
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<td>Lu-177</td>
<td>6.7d</td>
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<td>Cu-67</td>
<td>2.58d</td>
<td>beta/gamma</td>
<td>0.7mm</td>
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<tr>
<td>I-131</td>
<td>8.04d</td>
<td>beta/gamma</td>
<td>0.9mm*</td>
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<tr>
<td>Sm-153</td>
<td>1.95d</td>
<td>beta/gamma</td>
<td>1.2mm</td>
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<tr>
<td>Re-186</td>
<td>3.8d</td>
<td>beta/gamma</td>
<td>1.8mm</td>
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<tr>
<td>P-32</td>
<td>14.3d</td>
<td>beta</td>
<td>2.9mm</td>
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<tr>
<td>Re-188</td>
<td>17h</td>
<td>beta/gamma</td>
<td>3.5mm</td>
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<td>In-114m</td>
<td>50d</td>
<td>beta/gamma</td>
<td>3.6mm</td>
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<tr>
<td>Y-90</td>
<td>2.67d</td>
<td>beta</td>
<td>3.9mm</td>
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*Alan Perkins, University of Nottingham, UK*
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Current Radionuclide Therapies

- **Oncology**
  - Thyroid cancer: I-131
  - Non-Hodgkin’s Lymphoma: I-131, Y-90
  - Painful bone metastases: Sr-89, Sm-152
  - Hepatic metastases: Y-90
  - Neuroblastoma: I-131

- **Endocrine**
  - Hyperthyroidism: I-131

- **Hematology**
  - Polycythemia vera: P-32

- **Others**
  - Cystic craniopharyngioma: P-32
  - PVNS: P-32, Y-90
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• **Oncology**
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<table>
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<th>Radiopharmaceutical</th>
<th>Oncology</th>
<th>Endocrine</th>
<th>Hematology</th>
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<tr>
<td>I-131</td>
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</table>
I-131 Therapy for Thyroid Cancer

- Well established since the 1950s
- Beta and gamma rays
- Self-targeting
I-131/Y-90 Therapy for NHL

Jerry Russell
Sr-89 / Sm-152 therapy for painful bone metastases
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Neuroendocrine Tumors (NETs)

- Neuroendocrine tumors are neoplasms that arise from cells of the endocrine (hormonal) and nervous systems.
- Can be benign or malignant
- They most commonly occur in the intestine, but are also found in the lung and other parts of the body.

www.wikipedia.com
Octreoscan Imaging of NETs

- **Tracer:** In-111 Pentetreotide (OctreoScan)
- **Dose:**
  - Adult: 6 mCi
  - Pediatric: Adjust for age
- **Mechanism:** 8-amino-acid segment of somatostatin binds to somatostatin receptors expressed on neuroendocrine tumors
- **Indications:** Pituitary adenomas, carcinoid, gastrinoma, insulinoma, pheochromocytoma, medullary thyroid cancer, (N)SCLC, astrocytomas, meningiomas, neuroblastomas, lymphoma, breast, lung, RCC.
OctreoScan Imaging of NETs

Klinik für Nuklearmedizin, Universität Leipzig

10/2003  01/2004  04/2005
Accuracy of OctreoScan

- Carcinoid 80%
- Insulinoma 31%
- Gastrinoma 95%
- Glucagonoma 73%
- SCLC 100%
- Pheochromocytoma 100%
- Paraganglioma 86%
- Medullary thyroid Ca 54%
- VIPoma 86%
- Pituitary adenoma 80%
Peptide Receptor Radionuclide Therapy

- Peptide receptor radionuclide therapy (PRRT) started initially with $[^{111}\text{In}]-\text{DTPA}^0$-octreotide in the 1990s.
- Next generation: $[^{90}\text{Y}]-\text{DOTA}^0$-Tyr$^3$-octreotide (DOTATOC).
- Most recently: $[^{177}\text{Lu}]-\text{DOTA}^0$-Tyr$^3$-Octreotide (Lutathera®).
- $^{177}\text{Lu}$ is a medium-energy $\beta$-emitter with a maximum energy of 0.5 MeV and a maximal tissue penetration of 2 mm.
- Its half-life is 6.7 days.
- $^{177}\text{Lu}$ also emits low-energy $\gamma$-rays at 208 and 113 keV with 10% and 6% abundance, respectively.
Lutathera

- Lutathera® ([\(^{177}\text{Lu}\)-DOTA\(^0\)-Tyr\(^3\)-Octreotate]), is a radiolabeled somatostatin analog that can be used to treat metastatic gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs).

- GEP-NETs:
  - Carcinoid tumors (~2/3)
  - Pancreatic endocrine tumors (~1/3)

- Lutathera® kills these tumors by selectively targeting somatostatin receptors that are over-expressed on tumor cells.
Lutathera

- Lutathera® has been approved for pre-marketing sales in Greece, Portugal, Finland and Austria.
- Lutathera® has orphan drug status in Europe and the USA.
- A single Phase III protocol was submitted to both the FDA and EMA at the same time. Phase I/II results were based on an independent review of a large investigator-sponsored clinical study in over 600 patients affected by different Gastro Entero Pancreatic Neuro Endocrine Tumours (GEP-NETs) subtypes performed at the Erasmus Medical Centre, Rotterdam.
• Phase II results in progressive midgut carcinoid showed Progression-Free Survival of more than 44 months compared to the reported 14.6 months of Novartis' Sandostatin® LAR
• Lutathera® was shown to increase overall survival by between 3.5 and 6 years in comparison to current treatments, including chemotherapy.
• It was also shown to significantly improve quality of life.
Current Phase III Study

• The study, known as NETTER-1, is an international, multi-center, randomised, comparator-controlled, parallel-group study evaluating the efficacy and safety of Lutathera® compared to Novartis' Sandostatin® LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumors.

• **Sponsor:** Advanced Accelerated Applications

• **Indication:** Patients with inoperable, progressive, OctreoScan positive, well-differentiated neuroendocrine tumors of the small bowel (midgut carcinoid tumors), who are treated with 20 mg or 30 mg Octreotide LAR every 3-4 weeks at a fixed dose for at least 12 weeks prior to enrollment in the study.
Current Phase III Study

• **Primary objective:** To compare Progression Free Survival (PFS) after treatment with $^{177}$Lu-DOTA$^0$-Tyr$^3$-Octreotate plus best supportive care (30 mg Octreotide LAR) to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, progressive (as determined by RECIST Criteria), somatostatin receptor positive, well-differentiated neuroendocrine tumors of the small bowel (midgut carcinoid tumors).

• **Multiple secondary objectives:**
  – Objective Response Rate (ORR), Overall Survival (OS), Time to Tumor Progression (TTP), safety and tolerability of $^{177}$Lu-DOTA$^0$-Tyr$^3$-Octreotate, to evaluate health related Quality of Life (QoL), toxicity, dosimetry, pharmacokinetics, etc.
Practical Considerations

- 4 injections of Lutathera given every 8 +/- 1 weeks for a cumulative dose of 800 mCi.
- Remain at clinical site for 4-5 hrs after administration, and then must follow precautions to reduce radiation exposure to others.
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Prostate Cancer

- Most common cancer in men
- Second leading cause of cancer death in men
- Advanced prostate cancer often metastasizes to bone
- Since 2004, four systemic therapies are approved with mixed effects:
  - Docetaxel have direct antitumor effects may result in pain palliation but no decrease in skeletal-related events (SREs)
  - Zometa delays SREs without survival benefit
  - Samarium alleviates bone pain without survival benefit
  - Enzalutamide improves survival and palliative end-points without alleviating pain or SREs
Alpha particles

- α (Alpha particles)
- β (Beta particles)
- γ (Gamma rays)
Alpharadin

- Alpharadin (radium-223 chloride) is an experimental radiopharmaceutical to improve survival in patients with bone metastases from advanced cancer.
- Very short range of 2-10 cells and therefore causes less damage to surrounding tissues.
- Half life of 11.4 days, making it ideal for targeted cancer treatment. Any Alpharadin that is not taken up by the bone metastases is rapidly cleared to the gut and excreted.
- Indicated for castration resistant metastatic prostate cancer (mCRPC).
Alpharadin

- Self-targets to bone metastases by virtue of its properties as a calcium-mimic.

Comparison to Samarium and Strontium

Properties of selected radiopharmaceuticals for treatment of bone metastases in mCRPC

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Particle</th>
<th>Primary excretion</th>
<th>Physical half-life (days)</th>
<th>Particle energy in MeV</th>
<th>Tissue range (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radium-223 (^{223}<em>{36}) (Alpharadin\textsuperscript{®}) (^{38}</em>{38})</td>
<td>Alpha</td>
<td>Small bowel</td>
<td>11.4</td>
<td>5.56</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Samarium-153 (^{153}<em>{76}) (Quadramet\textsuperscript{®}) (^{76}</em>{76}) *</td>
<td>Beta</td>
<td>Kidney</td>
<td>1.9</td>
<td>0.81</td>
<td>3</td>
</tr>
<tr>
<td>Strontium-89 (^{89}<em>{71}) (Metastron\textsuperscript{®}) (^{77}</em>{77}) *</td>
<td>Beta</td>
<td>Kidney</td>
<td>50.5</td>
<td>1.46</td>
<td>8</td>
</tr>
</tbody>
</table>


- Decay of Radium-223:
  - 95.3% emitted as \(\alpha\) particles
  - 3.6% emitted as \(\beta\) particles
  - 1.1% emitted as photons
• **Phase II**: Found no significant side effects and showed 4.5 months increased OS, delayed SREs, and improvement in biochemical end points (PSA, total ALP).

• **Phase III**: Alpharadin successfully met the primary endpoint of OS in the ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer patients) study in 922 patients.

• **ALSYMPCA** was stopped early on the basis of achieving improvement in OS (two-sided p-value = 0.0022, HR = 0.699, the median overall survival was 14.0 months for Alpharadin and 11.2 months for placebo).
Current Early Access Trial in the US

- Patients diagnosed with symptomatic progressive bone predominant metastatic CRPC/HRPC with at least 2 skeletal metastases on bone scan with no lung, liver, and/or brain metastasis (lymph node metastasis is allowed)
- Life expectancy > 6 months; ECOG PS 0-2
- Adequate hematological, liver, and renal function
Practical Considerations

Photos by Paulo Castaneda
Practical Considerations

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Radiation/Release Considerations

- Since patients treated with Alpharadin emit negligible external radiation doses, they can be released immediately.
- For example, the average patient receiving 3.5 MBq (95 μCi) would have a dose rate at 1 m < 0.35 μSv/h (0.035 mrem/h).
- There are no restrictions on family contact after administration of Alpharadin. The range of α-particles in human tissue is approximately 0.1 mm.
- Once injected, α-particles are stopped by the patient’s tissue.
Summary

• Exciting time in the field of Nuclear Medicine and Molecular Imaging and in particular with Targeted Radionuclide Therapies

• Prior radionuclide therapies work well but mixed acceptance / usage

• Novel therapies with new radionuclides and carriers targeting new cancer indications holds great promise

• We discussed PRRT for NETs and Alpha emitter therapy for mCRPC; other therapies are also in the pipeline

• Increase in overall survival may be the key

• Acceptance / usage will remain important areas where we can have a role
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http://nuclearmedicine.stanford.edu

Thank You