New Radio Pharmaceuticals in the Diagnosis and Treatment of Neuroendocrine Tumors (NET)

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Disclosures

- Chairman & CEO of RadioMedix.
- Speaker Bureau/Consultant: Bayer Pharma, Endocyte, Curium.
- Sponsored research: Advanced Accelerator Applications (AAA), ImmunoMedix, Tekmira, Lantheous, RITA Foundation Houston.
Key Objectives:

1. Principles of targeted radiopharmaceuticals.
2. Classification of NET
3. Radiopharmaceuticals used in diagnoses of NET
4. Radiopharmaceuticals used in treatment of NET
5. Exciting clinical trials on newly developed targeted radioligand diagnostic and therapeutic agents in NEC.
Field of Nuclear Medicine

• **Diagnostics:** SPECT of PET
  - Functional evaluation of body organs
  - Functional probes for different disease processes or characteristics: receptors, antigens, proteins, metabolic pathways, etc.

• **Therapeutics:**
  Predominantly Oncology but there are also therapies for hyperthyroidism, RA, etc.
Principle of Targeted Radionuclide Diagnostic probes and Therapy agents In Oncology

- Carrying Diagnostic or Therapeutic radionuclides to a malignant site in order to detect (Diagnosis) or deliver lethal radiation dose to the tumors with minimal/Reversible injury to normal tissue (therapeutics) OR

"THERONOSTICS"

- WE SEE WHAT WE TREAT!
THERANOSTIC PAIRS
Targeted Molecular Imaging and Therapy
The Key-Lock Principle

Schematic Representation of a Drug for Imaging and Targeted Therapy
pharmacokinetics/biodistribution modifier

Target
Ligand
Linker
Chelator

Target

Antigens
e.g. CD20, HER2)

GPCR e.g. SSTR

Enzymes & inhibitors
e.g. PSMA

Transporters

Lock

Key

Molecular Address

Antibodies, minibodies,
Affibodies, SHALs, aptamers

Regulatory peptides
(agonists & antagonists)

Amino Acids

68Ga, 90Y, 177Lu

Reporting Unit

99mTc, 111In, 67Ga
64Cu, 68Ga
Gd3+

Cytotoxic Unit

90Y, 177Lu, 213Bi
105Rh, 67Cu, 186,188Re

Courtesy Helmut Mäcke (modified)
Advantages of the Targeted Radionuclide Therapy

- Identification of suitable candidates prior to treatment. “Personalized Therapy”
- Cross fire effect
- Higher efficacy, less side effects than conventional systemic chemotherapy.
- Radiation can be delivered to subclinical tumors and metastases that are too small to be imaged.
# Radioactive Decay Occurs by Three Main Processes

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Type of energy</th>
<th>Characteristics</th>
<th>Representative radionuclide</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>Particle</td>
<td>Release of 2 protons, 2 neutrons</td>
<td>Astatine 211, Pb/bismuth 212</td>
</tr>
<tr>
<td>β</td>
<td>Particle</td>
<td>Release of 1 electron</td>
<td>$^{131}$I, $^{90}$Y, Lu177</td>
</tr>
<tr>
<td>γ</td>
<td>Electromagnetic</td>
<td>Release of photons</td>
<td>$^{111}$IN, Tc$^{99}$m</td>
</tr>
</tbody>
</table>

Penetration of Particulate and Electromagnetic Radiation

Adapted from Wootton R. *Radiation Protection of Patients*. 1993.
**Alpha-particle versus beta-particle targeted radiotherapy**

### β-particles

- Intermediate energy (0.50-2.30 MeV) and long range in tissues (1-12 mm of tissue penetration).
- Path length correspond to clusters of cells (10 - 1,000 cells)

### α-particles

Radionuclides of interest in alpha-radionuclide therapy: ^225^Ac, ^213^Bi, ^212^Bi, ^211^At, ^223^Ra, or Alpharadin (Xofigo), ^212^Pb—which generates Bi^{212} and Po^{212}

- High energy (5-8 MeV) of alpha-particle and an intermediate path length (50-80 μm) in tissues
- Path length corresponds to the diameter of several cells (2-10 cells).
Currently available, FDA approved TNM Procedures

1. I-131 sodium iodide for treatment of hyperthyroidism, and thyroid cancer.

2. SR-89 chloride (Metastron ®) for treatment of painful osseous metastasis and adjuvant therapy of hormone refractory metastatic prostate cancer.

3. SM-153 EDTMP (Quadromet®) for treatment of painful osseous metastasis.

4. Y-90 Ibritumomab (Zevalin®) for treatment of CD-20 positive low grade NHL.
5. Y-90 SirSphere® for treatment of liver metastasis for colorectal cancer.


7. Xofigo (Ra-223 Chloride) for treatment of bone metastases in hormone refractory prostate cancer.

8. Lutathera® (Lu-177 DOTATATE) for SSTR expressing Neuroendocrine cancers.
Classics in Oncology:
Radioactive Iodine Therapy: Effect
On Functioning Metastases of
Adenocarcinoma of the Thyroid

S.M. Seidlin, MD
L.D. Marinelli, MA
Eleanor Ostrer

Therapy of neoplastic disease usually consists of two phases: first, the treatment of the primary focus and, second, that of metastases. Specifically, in adenocarcinoma of the thyroid, the primary site together with its immediate extensions is conventionally treated by surgery, radiation, or both. Distant metastases, if treated, are usually subjected to palliative external irradiation. This paper is a report of successful therapy of a case of metastatic adenocarcinoma of the thyroid treated by the principle of specific internal irradiation with radioactive iodine.

The earliest study of the uptake of radioactive iodine in two cases of carcinoma was reported by Hamilton and his associates in 1940. In 1942 he described two more cases in which tracer doses of radioactive iodine had been given to the patients prior to the removal of carcinomatous thyroids. Radioautographs of the excised glands showed no significant deposition of the radioactive iodine in malignant areas in any of these cases.

In April 1942, Keston, Ball, Frantz and Palmer reported the first positive evidence of pickup of the radioactive iodine by a metastasis from a carcinoma of the thyroid. In a patient with multiple lesions, Geiger counter measurements showed appreciable uptake of radioactive iodine in only one of the metastases. Subsequently, from the autopsy, these authors reported that "the bulk of the metastatic tissue was undifferentiated. The metastasis that showed consistent uptake of iodine was the only one that grossly resembled thyroid tissue and that, microscopically, showed chiefly well differentiated tumor."

Leiter, Seidlin, Marinelli and Baumann in a report of two cases of hyperthyroidism due to adenocarcinoma of the thyroid and to functioning metastases (one of which is the subject of the present paper) showed that the effect of thiouracil on the...
**Neuroendocrine Tumors (NET)**

- Heterogeneous group of tumors originating from Diffuse Endocrine System (DES)
- Carcinoid: foregut, midgut, hindgut.
- WHO Classification (2000): Well Differentiated and poorly differentiated NET.
- Somatostatin Receptor Expression - SSTR 1 to 5
- G1 (Ki up to 2%) G2(Ki >2,<20) G3(Ki>20)
Distribution of SST-Receptors in NETs

*in vitro studies*

- Gastrinoma, Glucagonoma 100%
- Insulinoma 72%
- Carcinoids 88%
- Paraganglioma 92%
- Medullary Thyroid Carcinoma 38%
- Small Cell Lung Cancer 57%
- Pheochromocytoma 73%

*Reubi et al. JNM 1999 adapted from Curr Med Chem 2000*
Theranostics in NET

• Neuroendocrine cancers

SSTR Imaging:

• \textit{In-111 Octreoscan}
• \textit{Ga-68/Cu-64 SSTR PET/CT}

Therapy:

• \textit{PRRT: Lu-177 or Y-90, or Alpha labeled PRRT}
Receptor Binding and Internalization

- Radionuclide
- Peptide analog
- Nucleus
- Endosome
- Lysosome
Advantages of Ga-68 DOTATATE

• Significantly higher spatial resolution.
• Quantification capability using MSUV for evaluation of response to therapy.
• The entire study is done in less than 2 hours.
• Less radiation than Octreoscan.
• Co-registration with CT scan


177Lu-DOTyr3-octreotate therapy in GEP Tumors: Antitumor Effects 3 m Follow-up

<table>
<thead>
<tr>
<th>Tumor</th>
<th>CR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>PD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>1 (1%)</td>
<td>41 (22%)</td>
<td>31 (17%)</td>
<td>78 (42%)</td>
<td>37 (20%)</td>
<td>188</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4 (6%)</td>
<td>26 (36%)</td>
<td>13 (18%)</td>
<td>19 (26%)</td>
<td>10 (14%)</td>
<td>72</td>
</tr>
<tr>
<td>Unknown Origin</td>
<td>10 (32%)</td>
<td>3 (10%)</td>
<td>7 (23%)</td>
<td>11 (36%)</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>Gastinoma/insulinoma</td>
<td>9 (47%)</td>
<td>4 (21%)</td>
<td>3 (16%)</td>
<td>3 (16%)</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>5 (2%)</td>
<td>86 (28%)</td>
<td>51 (17%)</td>
<td>107 (35%)</td>
<td>61 (20%)</td>
<td>310</td>
</tr>
</tbody>
</table>

*Kwekkeboom: EANM 2010*
IND: 78,256
Initial filing: June 2007
Final Approval: August 2010
**NETTER -1 Study Objectives and Design**

**Aim**
Evaluate the efficacy and safety of $^{177}$Lu-Dotatate + SSAs (symptoms control) compared to Octreotide LAR 60mg (off-label use)\(^1\) in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use).

**Design**

**Baseline and Randomization**
- **n = 115**
  - 4 administrations of 7.4 GBq of $^{177}$Lu-Dotatate every 8 weeks + SSAs (symptoms control)
- **n = 115**
  - Octreotide LAR (high dose - 60mg every 4 weeks\(^1\))

**Treatment and Assessments**
Progression free survival (RECIST criteria) every 12 weeks.

\(^1\) FDA and EMA recommendation

**Years follow up**
5
Progression-Free Survival

N = 229 (ITT)
Number of events: 91

177Lu-Dotatate: 23
Oct 60 mg LAR: 68

Hazard ratio: 0.21  
[0.13 – 0.33]  
\[p < 0.0001\]

79% reduction in the risk of disease progression/death

Estimated Median PFS in the Lu-DOTATATE arm \approx 40 months

\[\text{177}^\text{Lu-Dotatate} \text{ Median PFS: Not reached}\]

\[\text{Octreotide LAR 60 mg} \text{ Median PFS: 8.4 months}\]

All progressions centrally confirmed and independently reviewed for eligibility (SAP)
Future: Attempt For Cure!

• SSTR Anagontists
• High LET of alpha-particles

✓ Greater biological effectiveness TRT than conventional external beam x-ray radiation or beta emitters.

✓ Studies performed in cell culture have demonstrated that human cancer cells can be killed even after being hit by only a few alpha particles!

✓ Efficient cancer cell elimination can be achieved even in an hypoxic environment

• (unlike other types of radiation, where oxygen is necessary for generation of free radicals)
Improved imaging of neuroendocrine tumours with somatostatin receptor antagonists

$^{111}$In-DTPA-octreotide  $^{111}$In-DOTA-BASS  $^{111}$In-DOTA-JR11

Anterior  Posterior  Anterior  Posterior  Anterior  Posterior

Damian Wild et al. unpublished data.
Up to 11 times higher radiation dose to metastases with the Somatostatin Receptor antagonist

_Damian Wild et al. unpublished data_
No acute kidney, endocrine or hematologic toxicity higher than grade 0/I were observed after administration of ≤6 GBq per cycle.

Moderate hair loss occurred in 3 of 6 patients receiving single doses of 6 to 10 GBq;

1 case of radiation pneumonitis was observed in the patient receiving 10 GBq.

While morphologic long term response is still pending, shrinkage of primary tumors as well as liver and bone metastases has already been observed.

α-TRT using DOTATATE agents is a perfect choice for NET patients

Heidelberg University Group
AlphaMedix - Therapeutic $^{212}$Pb-labeled agent

*First FDA Permitted Clinical Trial*

- Excellent efficacy in animal models
- Favorable toxicity profile
- Dose optimization studies performed in animals
All patients (1 female and 5 male) received an average dose of 4.94 mCi of $^{203}$Pb-AR-RMX SPECT-CT scans acquired at 1 h, 4 h, 24 h and 48 h post injection.
$^{68}$Ga-DOTATATE PET/CT

$^{203}$Pb-AR-RMX SPECT/CT 4h (coronal) PT-006

$^{203}$Pb-AR-RMX SPECT
Future of TNM

- The menu on the approved agents will only increase.
- New agents will be based on targeting antigens, receptors, proteins, genes, etc.
- High dose Myeloablative therapy and Stem Cell transplant.
- Combination of Isotopes (short and long range).
- Combination of Targeted radiotherapy and Chemo.
- Chemotherapy as Radio-Sensitizer.
My Biases In R&D In Nuclear Oncology!

“Scratch where it is itching”

• UNMET NEEDS: NET, CRPC, Pancreatic adenocarcinoma, Metastatic Ovarian and colorectal Ca, GBM of the brain, etc.
• Combination of Alpha and Beta emitters for therapy and longer half life isotopes for PET.
• Therapeutic Nuclear Medicine is the wave of the future and demands to be a new sub-speciality.
THANK YOU!
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THANK YOU