Treatment of Neuroendocrine Tumors with Lu-177 Dotata®

Mark Tulchinsky, MD, FACNM, FSNMMI
Professor of Radiology and Medicine
Penn State University College of Medicine
Hershey, Pennsylvania

Mark.Tulchinsky@gmail.com

Disclosures, Conflicts of Interest:
• I Love Nuclear Medicine … so expect some bias (i.e. passion)
• I am not paid nor otherwise compensated by commercial entities for this presentation

Radioactive Iodine (RAI) Administration for Graves’ Disease: Birth of Theragnostics

Saul Hertz, M.D.
(April 30, 1905 – July 28, 1950)
• First to study RAI in an animal model of hyperthyroidism
• March 31st, 1941, at the age of 35 y, administered the first RAI treatment (RAIT) to a patient with Grave’s disease
• The first to use RAI uptake to inform RAIT, i.e. developed theragnostic principle
• Nuclear Medicine was born!

Thera(g)nostics

What’s in the Word?

• “Thera”, from Greek “therapeia” = healing & to heal, e.g. therapy
• “gnostic” is short for “gnostic”
• “Thera”, from Greek gnos = knowledge & to know, e.g. dia
• First, using diagnostic RF we image to know
  ✔ Does the target tissue bind the RF
  ✔ Dosimetry to optimize the therapy
• Second, using therapeutic RF we deliver the photons to heal diseased tissues

Abbr.: RF = radiopharmaceutical

131I Therapy of Hyperthyroidism

The First & Ideal Theagnostic Agent

• Measure activity in the patient’s thyroid by aiming the same uptake probe at the thyroid bed 24 hrs. later
• Calculate relative uptake as % of administered activity
• This is how much of administered 131I activity given for treatment will end up in the thyroid
• Calculate the desired activity based on this information, if and when the patient made a decision to be treated

Pre-RAIT Work-Up/Basics of Therapy: 24-Hr. 131I Uptake & 99mTcO4− Scan

• 24-Hr 131I uptake 43%
• 99mTcO4− Scan
  ✔ Graves’ Disease
• Neck palpation 35 g thyroid
• Calculation:
  ✔ None – fixed activity
  ✔ Radiation dose based activity
  ✔ Delivered activity per gram of thyroid

Hyperthyroidism: Treatment Goal

• RAIT Goals
  ✔ Euthyroidism – futile in Graves’ & hypothetically may increase carcinogenic risk – not recommended
  ✔ Ablation – predictable, time-saver for pts & dead cells don’t turn cancerous – recommended (1)
• Approach to Ablation
  ✔ Fixed dose (15 mCi) – simple, but not as predictable
  ✔ Radiation dose (cGy) based – multiday dosimetry makes it impractical, simplified is same as below
  ✔ Delivered activity per g of thyroid, normalized to 24hr uptake — simple, practical and rational (2)

Response to $^{131}$I Therapy in Graves': 0.24 mCi per gm of Thyroid
(PSU Experience – Prof. Mark Tulchinsky)

**Neuroendocrine Tumors: Introduction**

- Neuroendocrine Tumors (NETs) are a group of tumors originating in the neuroendocrine cells of many different organs
- NETs can remain clinically silent for years delaying the diagnosis
- While rare in comparison to breast or prostate cancers, they are the second most common type of gastrointestinal malignancy and increasing in incidence
- The estimated yearly incidence of NETs for the United States and the European Union combined is approximately 47,300
- NETs are classified as orphan diseases by the U.S. regulatory authorities
- From 1973 to 2004, incidence of NETs has grown by almost 500% (from 1.09/100,000 to 5.25/100,000 respectively)
- There are limited therapeutic options for advanced midgut NETs (20-45% of NETs) progressing on first-line somatostatin analogue therapy
- Thousands of patients have been treated with $^{177}$Lu-Dotatate peptide receptor radionuclide therapy (PRRT)

**Neuroendocrine Tumors: Epidemiology**

A growing population of patients
From 1973 to 2004, incidence of NETs has grown by almost 500% (from 1.09/100,000 to 5.25/100,000 respectively)

**Key Days:**
- Neuroendocrine Tumors: Introduction
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  - Thousands of patients have been treated with $^{177}$Lu-Dotatate peptide receptor radionuclide therapy (PRRT)
- Another term used for this and other similar treatments is Targeted Radionuclide Therapy (TRT)

**1.** Lawrence B, et al. 2011
**2.** Yao et al. 2008 - see abstract on 1st page. 
**2.** Yao et al: One hundred years after “carcinoid”: epidemiology of and prognostic factors for NET in 35,825 cases in the US. J. Clinical Oncology 26:3063-3072

**1.** Yao et al: One hundred years after “carcinoid”: epidemiology of and prognostic factors for NET in 35,825 cases in the US. J. Clinical Oncology 26:3063-3072
**2.** SEER: National Cancer Institute’s Surveillance, Epidemiology, and End Results

**NETs: Carcinoid Syndrome**

Constellation of symptoms mediated by various humoral factors secreted by NETs
- **Amines:** Serotonin, 5-HTP, NE, DA, Histamine
- **Polypeptides:** Kallikrein, Pancreatic Pp, Bradykinin, Motilin, Somatostatin, VIP, Neuropeptide K, Substance P, Neurokinin A & B, ACTH, Gastrin, GH, Peptide YY, Glucagon, ß-Endorphin, Neurotensin, Chromogranin A
- **Prostaglandins**

**Clinical Presentation of Carcinoid Syndrome**

(most common in Midgut NETs with liver mets)

1) Flushing ~ 85% of cases
2) Diarrhea ~ 80% of cases,
3) Carcinoid Heart ~ 60% of cases
   (Valvular lesions – Right Heart 40%, Left Heart 13%)
4) Bronchospasm ~ 20% of cases
5) Telangiectasia ~ 25% cases
6) Cyanosis ~ 18% cases

**Biomarkers for NET**

**Secretory NETs:**
- Serotonin, 5-HIAA (Carcinoid syndrome)
- Gastrin (Zollinger-Ellison syndrome)
- Insulin, Proinsulin, C-peptide (Hypoglycemia)
- VIP (severe diarrhea); Somatostatin (DM, gallstones)
- Glucagon (Glucagonoma); ACTH (Ectopic Chusing)

**Non-secretory NETs:**
- Chromogranin A (CgA) * (elevated in 60-100% of NET)
- Pancreatic Polypeptide (PP)
- Synaptophysin
- Neuron-specific enolase (NSE)
Overall Survival (OS) Metastatic NETs

- Highly variable OS in G1/G2 -M1 disease
- Median OS depends on the primary site:
  - Colon: 7 Mos
  - Lung: 17 Mos
  - Jejunum: 55 Mos
  - Ileum & Cecum: 65 Mos

53 year old woman presenting with acute onset of left lower quadrant pain with nausea and vomiting and abdominal lymphadenopathy of unclear etiology on CT:
- Chromogranin A 408 (ref <93)
- 24hr urine 5-HIAA 17.6 (ref <6)

Indications for ⁶⁸Ga-DOTATATE PET/CT

1) Localization of primary NET in adult and pediatric pts.
   - in a group of 131 pts with GEP NET of unknown primary
     - 95.2% detection rate with ⁶⁸Ga-DOTATATE
     - 45.6% detection rate with CT or MRI
     - 31% detection rate with ¹¹¹In Pentetreotide SPECT/CT
2) Staging and restaging of NET
3) Patient selection for PRRT:
   - VOI analysis: Tumor ⁶⁸Ga DOTATATE uptake > Liver
   - (Krenning scores 3 - 4)

Lutetium-177 (¹⁷⁷Lu), 6.64 d. Half-life
Excellent Theranostic Qualities

- Therapeutic β emissions (490 keV)
- Max tissue penetration ~2 mm
- Imaging γ & X-ray emission (113 keV & 208 keV)
- Allows documentation of uptake & dosimetry
- Pioneering work carried out in treating neuroendocrine tumors (NETs) with ¹⁷⁷Lu-labeled peptides at Erasmus Medical Centre, Rotterdam, the Netherlands
- Suitable for targeting small primary and metastatic tumors (e.g. prostate, breast, melanoma, lung, etc.)
- Currently used for therapeutic radiopharmaceuticals in treating NETs (FDA approved), prostate cancer (not FDA approved), etc.

177Lu-DOTATE

- ¹⁷⁷Lu-DOTATATE belongs to an innovative drug category called Peptide Receptor Radionuclide Therapy (PRRT). PRRT involves the systemic administration of a specific radiopharmaceutical to deliver cytotoxic radiation to a tumor (1)
- ¹⁷⁷Lu-DOTATATE is composed of a ¹⁷⁷Lu radionuclide chelated to a peptide. Lutetium emits high energy electrons (therapeutic photons) and gamma rays (imaging photon)
- The peptide is designed to target somatostatin receptors, which are overexpressed in approximately 80% of all NETs
- The affinity for SSTRs and the specificity of binding ensures a high level of specificity in the delivery of radiation to the tumor

Neuro Endocrine Tumors (NETs) Overview

- What are NETs?
- How are NETs diagnosed?
- How are NETs treated?
- Current Treatment Paradigms


2. Bergeveld et al. Best Practice & Res Clin Endocrinol Metab 2013, 26: 857-81
**Study Endpoints**

**Primary objective**

Compare Progression Free Survival (PFS) after treatment with 
177Lu-Dotatate plus 30 mg octreotide LAR vs treatment with high 
dose (60 mg) octreotide LAR

**Secondary objectives**

- Compare the Objective Response Rate between study arms
- Compare the Overall Survival between study arms
- Compare the Time to Progression between study arms
- Evaluate the safety and tolerability of 177Lu-Dotatate
- Evaluate the health related quality of life (QoL) as measured by 
  the EORTC QLQ-G11NET21 questionnaire

**Sites: 51 Centers in 11 Countries**

**NETTER -1 Study Objectives and Design**

**Aim**

Evaluate the efficacy and safety of 177Lu-Dotatate plus Octreotide/LAR 60 mg (off-label use) in patients with 
irreducible, somatostatin receptor positive, midgut NET, progressive under 
Octreotide LAR 30mg (label use)

**Design**

International, multicenter, randomized, comparator-controlled, parallel-group 
Phase III study conducted in 51 centers with 230 patients

**Treatment and Assessments**

- Progression free survival (PFS) interim every 12 weeks
- 3 Doses
  - Dose 1: Dose 2: Dose 3

**Baseline and Randomization**

- n = 115
- 4 administrations of 7.4 GBq of 177Lu-Dotatate every 8 weeks + Octreotide 30 mg
- 5 Years follow up

**Netter 1 Study: Inclusion Criteria**

- Patients ≥18 years of age
- Metastatic or locally advanced, inoperable, histologically proven, midgut NET
- Ki67 index ≤ 20% (Grade 1-2)
- Progressive disease on uninterrupted fixed dose of 
ocreotide LAR (20-30 mg every 3-4 weeks)
- Somatostatin receptor positive disease
- Karnofsky Performance Score ≥ 60
- Both functioning and non-functioning tumors

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Treatment of Neuroendocrine Tumors with Lu-177 Dotatate

 Patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>177Lu-Dotatate (n=16)</th>
<th>Octreotide LAR (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>53 (49%)</td>
<td>50 (57%)</td>
</tr>
<tr>
<td>Female</td>
<td>53 (51%)</td>
<td>53 (43%)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>63 ± 13</td>
<td>64 ± 10</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>25 ± 8</td>
<td>28 ± 7</td>
</tr>
</tbody>
</table>

Primary tumor site, n (%):
- Jejunum: 6 (5%) vs 5 (6%)
- Ileum: 86 (74%) vs 82 (73%)
- Appendice: 1 (1%) vs 2 (2%)
- Right colon: 3 (3%) vs 1 (1%)
- Other: 20 (17%) vs 19 (17%)

Site of metastasis, n (%):
- Liver: 97 (81%) vs 94 (83%)
- Lymph nodes: 77 (66%) vs 63 (58%)
- Bone: 13 (11%) vs 12 (11%)
- Lungs: 11 (10%) vs 5 (4%)
- Other: 40 (33%) vs 37 (33%)

79% Risk Reduction for disease progression/death
Median PFS in DOTATATE arm: 40 Mos

Hematology indices: WBC

Hematology indices: Lymphocytes

Hematology indices: Platelets

Renal Function Stability – 2 yrs observation

Progression Free Survival

Overall Survival

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PRRT: Long-Term Hematologic Toxicity

In Phase III Erasmus Study (Europe): 615 pts
- Myelodysplastic Syndrome (MDS) suspected to be related to 177Lu-DOTATATE occurred in five patients (5/615 pts = 0.008%), diagnosed at 1 to 3 yrs after treatment
- Acute leukemia was reported for 3 pts., diagnosed up to 7 years after the last 177Lu-DOTATATE treatment with a cumulative administered activity of either 22.2 GBq (600 mCi; 1 patient) or 29.6 GBq (800 mCi; 2 patients).

PRRT: Long-Term Hematologic Toxicity

Sub-analysis of the hematological data has been conducted on the 367 Dutch patients for whom a longer follow-up was available:
- Leukopenia grade 3-4 occurred in 4.1% of pts.
- Anemia grade 3-4 occurred in 4.9% of pts.
- Thrombocytopenia grade 3-4 occurred in 7.3% pts

Safety/Tolerability

<table>
<thead>
<tr>
<th>Any adverse event</th>
<th>177Lu-Dotatate (n=615)</th>
<th>Octreotide LAR (n=615)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related to treatment</td>
<td>106 (86%)</td>
<td>95 (88%)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>29 (24%)</td>
<td>20 (24%)</td>
</tr>
<tr>
<td>Related to treatment</td>
<td>10 (9%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>7 (8%)</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>Related to treatment</td>
<td>5 (5%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

The World Association of Radiopharmaceutical and Molecular Therapy position statement on the initial radioiodine therapy for differentiated thyroid carcinoma


Conclusions

- 177Lu-Dotatate therapy is generally well tolerated and offers patients with terminal disease much increased progression free survival after all else fails
- The administration takes 6-7 hours of visiting an infusion room, repeated 4 times (cycles), 8 weeks between the cycles
- This is the first of many new theranostic agents in the process of being approved by the FDA
- The next expected agent will be for prostate cancer treatment