Peptide Receptor Radio-Nuclide Therapy (PRRNT) as a Novel, Rationale Option of Care for Metastatic NETs

Presented by

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Conflict of Interest

- No commercial conflicts to declare
- May discuss products under INDs
- Research supported by:
  - NCI RO1 CA167632
  - NCI SPORE P50 CA174521

Thomas M. O’Dorisio
TTP = Time to Progression

PATIENT

OctreoScan® Ga-68-DOTATOC PET
\(^{123\text{I}}/^{131\text{I}}\)-MIBG

Iowa Neuroendocrine Database (INED) Registry
- 1700 subjects

Somatostatin Congener Octreotide, Somatuline

Traditional Surgery or Gamma Probe Guided Surgery

H.A.E.
Bland Hep Art Embo SIR Spheres Therapy

Clinical Trials Anti-angiogenics mTOR Inhibitors

Pathology Tissue Diagnosis

Peptide Receptor Radio-Nuclide Therapy (P.R.R.N.T.) (Y90/Lu177-DOTATOC/TATE)

Conventional Chemo

Liver Transplant

+ve

Theranostics

Ga-68-DOTATOC PET

(-)

FDG-PET

(+)

TTP = 3-4 yrs

TTP = 17 mo

TTP = 7 mo

TTP = 3-5 yrs

TTP = 4-5 yrs

SST\(_2\) Receptor Stains and Expression Blood Biomarkers

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Targeted Molecular Imaging and Therapy

Maintain High Affinity SST2 receptor

Somatostatin Analogs

Stable Radiometal Binding In Vivo

Imaging • $^{64}Cu$, $^{68}Ga$

Therapy • $^{90}Y$, $^{177}Lu$

Courtesy Helmut Maecke, University Hospital, Basil CH
Current Targeting Paradigm
One Receptor – One Ligand

- High receptor expression
- Native peptide sequence known
- High affinity/specificity/avidity for target
- Synthetically feasible (<50 residues)

Concept & design by M Schultz
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Evolution of Neuroendocrine Medical Therapy

- Secretin: 1902
- Insulin: 1921
- CCK: 1925
- Gastrin: 1905
- “Karzinoide”: 1907
- Endocrine Cell (Helle Zellen): 1938
- Zollinger-Ellison Syndrome: 1955
- Gastrin Purified: 1961
- GIP: 1971
- Somatostatin Purified: 1973
- Octreotide: 1980
- VIP: 1972
- I-131 Therapy: 1930
- Verner-Morrison Syndrome: 1958
- Radio-Peptide Receptor (RPR): 1967
- RIA: 1960
- OctreoScan® (RPR Imaging): 1990
- OctreoScan® Guided Surgery: 1991
- RPR Guided Therapy: 1994
- Gallium 68 RPR-PET: 2000

THERANOSTICS (R.P. Baum): 2011

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Teresa Ruggle
Dawn Wray
Evolution of Neuroendocrine Medical Therapy

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Affinity Profiles (IC$_{50}$) of a Series of Somatostatin Analogues to the Subtypes of Human Somatostatin Receptors (sstr 2-5)

<table>
<thead>
<tr>
<th>Peptide</th>
<th>sstr2</th>
<th>sstr3</th>
<th>sstr4</th>
<th>sstr5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS-28</td>
<td>2.7</td>
<td>7.7</td>
<td>5.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Octreotide</td>
<td>2.0</td>
<td>187</td>
<td>&gt;1000</td>
<td>22</td>
</tr>
<tr>
<td>DTPA Octreotide</td>
<td>12</td>
<td>376</td>
<td>&gt;1000</td>
<td>299</td>
</tr>
<tr>
<td>DOTA-[Tyr$^3$] octreotide</td>
<td>14</td>
<td>27</td>
<td>&gt;1000</td>
<td>103</td>
</tr>
<tr>
<td>Ga-DOTA [Tyr$^3$] octreotide</td>
<td>2.5</td>
<td>613</td>
<td>&gt;1000</td>
<td>73</td>
</tr>
<tr>
<td>y-DOTA - [Tyr$^3$] octreotide</td>
<td>11</td>
<td>389</td>
<td>&gt;10,000</td>
<td>114</td>
</tr>
<tr>
<td>DOTA- [Tyr$^3$] octreotate</td>
<td>1.5</td>
<td>&gt;1000</td>
<td>453</td>
<td>547</td>
</tr>
<tr>
<td>Ga-DOTA-[Tyr$^3$] octreotate</td>
<td>0.2</td>
<td>&gt;1000</td>
<td>300</td>
<td>377</td>
</tr>
<tr>
<td>Y-DOTA [Tyr$^3$] octretate</td>
<td>1.6</td>
<td>&gt;1000</td>
<td>523</td>
<td>187</td>
</tr>
</tbody>
</table>

In-11 DTPA Octreotide

Ga-68 DOTA Tyr3- Octreotide
$^{90}\text{Y} \text{DOTATOC}$

$\text{DOTA-CO-NH-D-Phe-Cys} \quad \text{Tyr}$

$\text{S} \quad \text{S} \quad \text{S}$

$\text{Thr(ol)-Cys} \quad \text{Thr}$

$\text{D-Trp} \quad \text{Lys}$

$^{177}\text{Lu} \text{DOTATATE}$

$\text{DOTA-CO-NH-D-Phe-Cys} \quad \text{Tyr}$

$\text{S} \quad \text{S} \quad \text{S}$

$\text{Thr-Cys} \quad \text{Thr}$

$\text{D-Trp} \quad \text{Lys} \quad \text{Lu}$
Subject 2

Ga-68 DOTATOC

In-111 Octreotide

Menda et al.
Subject 4

In-111 Octreotide

Ga-68 DOTATOC

MIP

Menda et al.
Subject 5

In-111 Octreotide

Ga-68 DOTATOC

Menda et al.
Unknown Primary with Metastatic NET to Liver and Bones, Negative Octreoscan and CT for Primary
## Contrast between Octreoscan & Ga-68 DOTATOC-PET

<table>
<thead>
<tr>
<th></th>
<th>In-111 DTPA Octreotide (Octreoscan) SPECT</th>
<th>Ga-68 DOTA Octreotide PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution</td>
<td>10-15 mm</td>
<td>4-6 mm</td>
</tr>
<tr>
<td>Binding Affinity * (IC50)</td>
<td>22 ± 3.6</td>
<td>2.5 ± 0.5 (TOC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 ±0.04 (TATE)</td>
</tr>
<tr>
<td>Radiation Dose to Pt</td>
<td>2.6 rem</td>
<td>0.4 rem</td>
</tr>
<tr>
<td>Radioisotope Production</td>
<td>Cyclotron</td>
<td>Generator</td>
</tr>
<tr>
<td>Convenience</td>
<td>2 day procedure; 3 visits</td>
<td>90min procedure, single visit</td>
</tr>
</tbody>
</table>

PRRNT

- **Peptide** – DOTA[tyr $^3$] Octretide/Octreotide
- **Receptor** – sst 2
- **Radio-Nuclide** – $^{90}$Y or $^{177}$Lu
- **Therapy**
90Y-Edotreotide
(90Y-DOTA-DPhe1-Tyr3-Octreotide)
(90Y-DOTATOC)
(Onalta™/OctreoTher™)

\[ 90Y \text{-DOTA}^\text{D} \rightarrow \text{Phe-Cys-Tyr-dTrp-Lys-Thr}_{\text{OL}}-\text{Cys-Thr} \]

\((\text{SMS} \, 204-090)\)

\[ 90Y = 90\text{Yttrium}, \text{high energy beta, 5mm range, physical half-life, 64.1 hours} \]

\[ \text{DOTA} = 1, 4, 7, 10-\text{Tetraazacyclododecane-N, N}^I, N^II, N^III, \text{-tetra-acetic acid} \]

\[ 90Y-\text{DOTA} = \text{Complex, dissociation constant } 10^{-25} \]
Killing a tumor with molecular targeting
$^{90}\text{Y}$
90Y-Edotretotide for Metastatic Carcinoid Refractory to Octreotide

DL Bushnell, TM O’Dorisio, MS O’Dorisio, Y Menda, RJ Hicks, E Van Cutsem, JL Baulieu, F Borson-Chazot, L Anthony, AB Benson, K Oberg, AB Grossman, M Connolly, H Bouterfa, Y Li, KA Kacena, N LaFrance and SA Pauwels

From the Dept. of Radiology, Div. of Nuclear Medicine, the Dept. of Internal Medicine, Div. of Endocrinology, and Dept. of Pediatrics, Div. of Pediatric Hematology/Oncology, University of Iowa, Roy J. and Lucille A. Carver College of Medicine; Iowa City Veterans Administration Medical Center, Diagnostic Imaging and Radioisotope Therapy Service, Iowa City IA; Peter MacCallum Cancer Institute, East Melbourne, Victoria, Australia; Digestive Oncology Unit, University Hospital Gasthuisberg, 3000 Leuven, Belgium; Service de Medecine Nucleaire, Paris; Centre de Medecine Nucleaire, Hospices Civils et Universite de Lyon; Institut Gustave Roussy, Villejuif, France; Louisiana State University Health Sciences Center, New Orleans, LA; Div. of Hematology-Oncology, Northwestern University, Chicago, IL; Medicinkliniken, Endokrin-Oncol enh, UAS, Uppsala, Sweden; Dept. of Endocrinology, St Bartholomew’s Hospital, London, England; Novartis Pharmaceutical Corporation, East Hanover, NJ; Molecular Insight Pharmaceuticals, Cambridge, MA; and Cliniques Universitaires Saint-Luc, Service de Medecine Nucleaire, Brussels, Belgium


Purpose

To evaluate the clinical effect of 90Y-Edotreotide to treat symptomatic somatostatin congener refractory, progressing carcinoid tumor patients.
Study Population

Eligibility:

• One or more symptoms uncontrolled despite optimal somatostatin analog therapy.

• Metastatic disease identified by Grade 3 or 4 (Krenning) $^{111}$In-pentatetreotide (OctreoScan®)

• At least one CT/MR measurable site demonstrating progression, per Southwest Oncology Group (SWOG)

• Creatinine < 1.7mg/dl (<150 μmoL/L)

Karnofsky performance status (KPS) ≥ 60
## Selected Demographics of 90 Patients Enrolled Between July 20, 2001 & August 19, 2002

<table>
<thead>
<tr>
<th></th>
<th>Mean 59.8 ± 12 (S.D.) (range 18-88)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35 (39%)</td>
</tr>
<tr>
<td>Male</td>
<td>55 (61%)</td>
</tr>
<tr>
<td><strong>Prior Surgery</strong></td>
<td>77 (86%)</td>
</tr>
<tr>
<td><strong>Prior Anti-Cancer Therapy</strong></td>
<td>40 (44%)</td>
</tr>
<tr>
<td><strong>Liver METS at Baseline</strong></td>
<td>65 (72%)</td>
</tr>
<tr>
<td><strong>Octreotide use at Baseline</strong></td>
<td>No 27 (30%)</td>
</tr>
<tr>
<td></td>
<td>Yes 63 (70%)</td>
</tr>
<tr>
<td><strong>90Y-Edotretotide Therapy</strong></td>
<td>73 (81%)</td>
</tr>
<tr>
<td>All 3 doses (120mCi per dose)</td>
<td></td>
</tr>
<tr>
<td>2 doses</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>1 dose</td>
<td>9 (10%)</td>
</tr>
</tbody>
</table>

Safety Results

- 90 patients experienced one or more adverse effects with majority [76 (84%)] GI events of nausea, vomiting, diarrhea, all reversible

- Of 90 patients, 54 (60%) had grade 3-4 adverse events with lymphopenia, nausea, vomiting

- Three of 90 patients (3.3%) experienced reversible grade 3 to 4 renal toxicity all lasting < 45 days
## Demographics of Selective Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>79 Evaluable (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>65 (82%)</td>
</tr>
<tr>
<td>Flush/Flash</td>
<td>63 (80%)</td>
</tr>
<tr>
<td>Fatigue (tired)</td>
<td>75 (95%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>62 (79%)</td>
</tr>
<tr>
<td>Weakness (↓ strength)</td>
<td>62 (79%)</td>
</tr>
<tr>
<td>Pain (muscle/joints)</td>
<td>47 (60%)</td>
</tr>
</tbody>
</table>

Medication

- $^{90}$Y-edotreotide (OCTREOTher®, Onalta®, Molecular Insight Pharmaceuticals), infused over 10-15 min.

- Three doses, fixed, 4.4 GBq (120 mCi) administered at 6-9 week cycles; Total 360 mCi.

- Two liters of amino acid solution (Aminosyn II, Abbott Labs, Illinois, or equivalent) with 28g of both lysine and arginine (800M OsmoL/L) i.v., at 500ml/h over 4 hours.
Kaplan Meier analysis for patients with durable diarrhea response

Percentage of progression-free patients

Months since first dose

Logrank statistic comparing patients with and without a reduction in diarrhea symptoms: p=0.031

Patients with a reduction in diarrhea symptoms, n=29

Patients with no diarrhea symptoms at baseline, n=10

Patients WITHOUT a reduction in diarrhea symptoms, n=12

Median of improved diarrhea = 18.2 mon

Median of unimproved diarrhea = 7.9 mon

Tumor Status

- Response based on the intent-to-treat; 90 patients entered on study
- No complete response (CR)
- Four (4.4%), unconfirmed, partial response (PR)
- 63 (70%) stable disease (SD)
- 67 (74%) objectively stable or responding
- 11 (12.2%) had disease progression (DP)
## Modified Linear Trend for Symptoms and QOL (using Health Thermometer, N=90)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Baseline mean with symptoms*</th>
<th>18 weeks after Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>3.0</td>
<td>1.4, p&lt;.001</td>
</tr>
<tr>
<td>Hot Flashes</td>
<td>2.7</td>
<td>1.4, p&lt;.001</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>2.6</td>
<td>0.9, p&lt;.001</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1.9</td>
<td>-0.2, p&lt;.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.3</td>
<td>2.3, p&lt;.001</td>
</tr>
<tr>
<td>Pain (muscles/joints)</td>
<td>2.5</td>
<td>1.2, p&lt;.001</td>
</tr>
</tbody>
</table>

* Likert scales (0, not bothered; 6 extremely bothered)

Conclusion

$^{90}$Y-edotretotide offers an advantageous benefit to risk profile for patients with metastatic carcinoid tumor refractory to octreotid therapy.
Evolution of Neuroendocrine Medical Therapy

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Theranostics

“Molecular targeting of VECTORS which can be used for both therapies and diagnosis, when modified accordingly…

(it) embodies both molecular and personalized medicine.”

DOTA-DPhe\(^1\)-Tyr\(^3\)-Octreotide (DOTA-TOC/TATE)

Theranostic Application

**Isotope**-DOTA-Phe-Cys-Tyr

\[ \text{Isotope-DOTA-Phe-Cys-} \]

\[ \text{Tyr} \]

\[ \text{Lys} \]

\[ \text{Thr}_{\text{OL}} \]

\[ \text{Cys-} \]

\[ \text{Thr} \]

(SMS 204-090)

**Isotope** (Radiometal):

- \( \text{Ga}^{68} \)-DOTA-TOC-PET: sensitive; quantifiable
- \( \text{Y}^{90} \)-DOTA-TOC: hard beta; 7-9 mm range “kill”
- \( \text{Lu}^{177} \)-DOTA-TOC: soft beta; 3-5 mm range “kill”
Neuroendocrine Tumor Faculty

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