The Many Uses of Somatostatin Analogs in the Management of Neuroendocrine Tumors

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Pharmacy Grand Rounds
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Learning Objectives

• Recognize carcinoid symptoms in patients diagnosed with functional neuroendocrine tumors

• Discuss current evidence for treatment with somatostatin analogs in neuroendocrine tumors

• Define the patient population that would benefit from somatostatin analogs
Neuroendocrine tumors (NETs)

- Solid malignant tumors originate from neuroendocrine cells
- Annual incidence in the United States ranges between two and five per 100,000 patients
- Most commonly in patients aged 60-70
Tumor Classification

• Location
• Functional or non-functional
• Pathological grade and differentiation
  • Well and poorly differentiated
  • Ki-67 (Grade 1-3)

Barakat MT, Meeran K, Bloom SR. Endocr Relat Cancer. 2004
Locations of Neuroendocrine Tumors

**Foregut**
- Thymus
- Esophagus
- Lung
- Stomach

**Midgut**
- Appendix
- Ileum
- Cecum

**Hindgut**
- Distal large bowel
- Rectum

**Pancreatic**
- Insulinoma
- Glucagonoma
- VIPoma
Functional versus Non-Functional

Functional NET
- Releases hormones that result in endocrine hyperfunction syndromes

Non-Functional NET
- Lack of endocrine symptoms

Chung C. Am J Health Syst Pharm. 2016
Barakat MT, Meeran K, Bloom SR. Endocr Relat Cancer. 2004
Diagnosis of Neuroendocrine Tumors

- Biopsy
- Blood/Urine Testing
  - Chromogranin A
  - Synaptophysin
  - Serotonin (urinary 5HIAA)
  - Neuropeptide K
- EGD
- Imaging
- Somatostatin Receptor Screening
- Signs/Symptoms
Recognize carcinoid symptoms in patients diagnosed with functional neuroendocrine tumors
Carcinoid Syndrome

- Vasoactive Flushing
- Sweating
- Hyper/Hypotension
- Chronic Diarrhea
- Wheezing
- Carcinoid Heart Disease

Barakat MT, Meeran K, Bloom SR. Endocr Relat Cancer. 2004
NET Management

Anti-Proliferation
- Surgical resection
- Chemotherapy
- Radiotherapy
- Chemoembolization
  - Somatostatin analogs
- mTOR inhibitors

Symptoms
- Cholestyramine
- Loperamide
- Telotristat
  - Somatostatin analogs
- Valve replacement surgery
Somatostatin Analog Mechanism of Action

- Bind to somatostatin receptors (SSTR) that are overexpressed in the tumor tissue.

<table>
<thead>
<tr>
<th>Somatostatin analogs</th>
<th>Adenylyl Cyclase</th>
<th>cAMP</th>
<th>Nucleus</th>
<th>Proliferation</th>
<th>Secretion</th>
</tr>
</thead>
</table>

Kunz PL. J Clin Oncol. 2015
Chung C. Am J Health Syst Pharm. 2016
**Somatostatin Analogs (SSAs)**

- Mainstay of treatment for functional NETs
- Octreotide, Lanreotide, Pasireotide

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide SA</td>
<td>Carcinoid Symptoms</td>
<td>• Nausea, diarrhea, abdominal cramps, hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cholelithiasis/biliary sludging</td>
</tr>
<tr>
<td>Octreotide LAR</td>
<td>Carcinoid Symptoms</td>
<td></td>
</tr>
<tr>
<td>Octreotide LAR</td>
<td>Anti-proliferation</td>
<td></td>
</tr>
<tr>
<td>Lanreotide LAR Autogel</td>
<td>Carcinoid &amp; Anti-proliferation</td>
<td></td>
</tr>
</tbody>
</table>

SA: Short Acting  
LAR: Long Acting Repeatable
Question 1

CK presented to the hospital with intermittent flushing, loss of appetite, and general malaise.
Question 1

Which of these may warrant the addition of octreotide for carcinoid symptoms?

A. Vasoactive Flushing
B. Loss of appetite
C. Malaise
D. All of the above
Discuss current evidence for treatment with somatostatin analogs in neuroendocrine tumors
# PROMID Trial

<table>
<thead>
<tr>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, randomized, double-blind, placebo-controlled, phase 3 trial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>85 patients, functional and non-functional midgut NETs, median age 62</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Interventions</th>
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<tr>
<td>Patients assigned in a 1:1 ratio to receive either: Octreotide LAR 30 mg IM or Placebo every 28 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>To determine if octreotide LAR prolongs time to tumor progression and survival</td>
</tr>
</tbody>
</table>
# PROMID: Patient Population

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>85</th>
</tr>
</thead>
</table>
| Tumor Type | Metastatic midgut  
| Functional & non-functional |
| Tumor Prognosis | Well-differentiated  
| Low hepatic tumor load  
| 95% had Ki-67 up to 2% (Grade 1) |
| Inclusion Criteria | Locally inoperable NET  
| Karnofsky score > 60% |
| Exclusion Criteria | Pretreatment with SSA for ≥ 4 weeks  
| Pretreatment with interferon alpha  
| Chemotherapy or chemoembolization |
PROMID: Time to Tumor Progression

Log-rank test stratified by functional activity: $P = .000072$, HR = 0.34 (95% CI, 0.20 to 0.59)

PROMID: Overall Survival

Log-rank test stratified by functional activity: $P = .77$, HR = 0.81 (95% CI, 0.30 to 2.18)
PROMID: Author’s Conclusions

- Octreotide LAR inhibits tumor growth in patients with functional and non-functional midgut NETs
- Survival analysis was non-confirmatory
- Largest benefit in patients with resected primary tumor and low hepatic tumor load
- Most frequently observed adverse events with octreotide were fever and fatigue
PROMID: Limitations

- Small patient size
- Patient population
- Short follow up time
## CLARINET Trial

<table>
<thead>
<tr>
<th>Study design</th>
<th>Prospective, randomized, double-blind, placebo-controlled, multinational study</th>
</tr>
</thead>
</table>
| Participants | 204 Patients, median age 63  
|              | • Advanced, well-differentiated, or moderately differentiated tumors  
|              | • Non-functional only |
| Interventions| Patients assigned in a 1:1 ratio to receive either:  
|              | Lanreotide LAR Autogel 120 mg SQ or Placebo every 28 days for 96 weeks |
| Primary outcome | Progression-free survival (PFS) |
## CLARINET: Patient Population

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>• 204</th>
</tr>
</thead>
</table>
| Tumor Type         | • Pancreatic, midgut, hindgut, or unknown origin  
|                    | • Non-functional only  
|                    | • Somatostatin receptor positive |
| Tumor Prognosis    | • Locally advanced or metastatic  
|                    | • Low-grade, well or moderately differentiated  
|                    | • Ki-67 <10% (Grades 1 and 2) |
| Inclusion Criteria | • Unresectable tumor |
| Exclusion Criteria | • Pretreatment with interferon alpha  
|                    | • Chemo or chemoembolization, radionuclide or SSA  
|                    | • Major surgery within three months |
CLARINET: Progression-Free Survival

- Lanreotide 120 mg
  - 32 events, 101 patients
  - Median not reached

- Placebo
  - 60 events, 103 patients
  - Median, 18.0 mo (95% CI, 12.1–24.0)

- P<0.001 for the comparison of progression-free survival
- Hazard ratio for progression or death: 0.47 (95% CI, 0.30–0.73)

## CLARINET Results

### Table 2. Secondary Efficacy End Points (Intention-to-Treat Population)\(^*\)

<table>
<thead>
<tr>
<th>End Point</th>
<th>Lanreotide (N = 101)</th>
<th>Placebo (N = 103)</th>
<th>Between-Group Comparison (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients alive without disease progression — no./total no. (%)(^†)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At wk 48</td>
<td>67/101 (66)</td>
<td>50/103 (49)</td>
<td>2.11 (1.19 to 3.76)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>At wk 96</td>
<td>53/101 (52)</td>
<td>26/103 (25)</td>
<td>3.27 (1.81 to 5.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to tumor progression (95% CI) — mo(^‡)</td>
<td>Not reached</td>
<td>18.0 (12.1 to 24.0)</td>
<td></td>
<td>&lt;0.001(^§)</td>
</tr>
<tr>
<td>EORTC QLQ-C30 global health status score — least-squares mean change from baseline to last post-baseline value available(^¶)</td>
<td>-5.18±3.73</td>
<td>-4.87±3.7</td>
<td>-0.31±2.74 (-5.73 to 5.10)</td>
<td></td>
</tr>
<tr>
<td>Patients with ≥50% reduction in level of chromogranin A from baseline to last post-baseline level available — no./total no. (%)(^‖)</td>
<td>27/64 (42)</td>
<td>3/64 (5)</td>
<td>15.20 (4.29 to 53.87)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CLARINET: Author’s Conclusions

• Lanreotide was associated with significantly prolonged PFS in patients with metastatic NETs of grade 1 or 2

• Similar proportions of patients in the two groups had adverse effects
  • Most common adverse effect with lanreotide was diarrhea
CLARINET: Limitations

- Low grade tumors
- Non-functional tumors only
- Patient population
Question 2

CK was diagnosed with a non-functional NET located in her midgut. This tumor was labeled locally inoperable. She has not displayed carcinoid symptoms.
Question 2

Based on the primary literature, would you consider starting a somatostatin analog in this patient for anti-proliferation?

A. Yes

B. No
Key Points: PROMID vs. CLARINET

• Octreotide vs. Lanreotide
• Different tumor prognoses
• Functional vs. nonfunctional tumors
• Time to tumor progression vs. Progression-free survival
Define the patient population that would benefit from somatostatin analogs
Who Should Get Somatostatin Analogs?

- Patients with carcinoid symptoms
- Patients with functional, unresectable NETs for anti-proliferation
- Patients with non-functional, unresectable NETs for anti-proliferation
Future Direction

• Peptide Receptor Radionuclide Therapy
• Lutetium ($^{177}$Lu) oxodotreotide (Lutathera®)

**Phase 3 Trial of $^{177}$Lu-Dotatate for Midgut Neuroendocrine Tumors (NETTER-1 Trial)**

- $^{177}$Lu-Dotatate IV + octreotide LAR 30 mg IM vs. octreotide LAR 60 mg IM
- Longer progression free survival, higher response rate
- Myelosuppression in <10% of patients

Question 3

Which of the following patients may benefit from somatostatin analog therapy?

A. AL, has an unresectable, non-functional NET
B. BP, has unresectable, widely metastatic, functional NET
C. CS, has a functional NET with carcinoid symptoms
D. All of the above
Summary

• NETs are a heterogeneous group of tumors
• NETs can be functional or non-functional
• Functional NETs display carcinoid symptoms
  • Vasoactive flushing, diarrhea, etc.
• Octreotide and lanreotide can both be used for carcinoid symptoms and as anti-proliferative agents
Questions & Discussion
The Many Uses of Somatostatin Analogs in the Management of Neuroendocrine Tumors

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Pharmacy Grand Rounds
October 24, 2017
Cost

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mayo Acquisition Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide Short Acting 150 mcg, 300 mcg</td>
<td>$15.38, $29.02</td>
</tr>
<tr>
<td>Octreotide LAR 30 mg</td>
<td>$4,277.77</td>
</tr>
<tr>
<td>Lanreotide LAR 120 mg</td>
<td>$43.26</td>
</tr>
</tbody>
</table>
## Management of Carcinoid Tumors

### Unresectable and/or Metastatic NET of the GI Tract
- 5-FU
- Capecitabine
- Dacarbazine
- Oxaliplatin
- Streptozocin
- Temozolomide
- Everolimus
- Interferon alfa 2b

### Unresectable and/or Metastatic NET of Lung/Thymus
- Everolimus
- Temozolomide
- Cisplatin or Carboplatin + Etoposide
# Staging of Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Primary Tumor</th>
<th>Regional Lymph Nodes</th>
<th>Distant Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TX</strong></td>
<td><strong>NX</strong></td>
<td><strong>M0</strong></td>
</tr>
<tr>
<td>Cannot be assessed</td>
<td>Cannot be assessed</td>
<td>No distant metastases</td>
</tr>
<tr>
<td><strong>T0</strong></td>
<td><strong>N0</strong></td>
<td><strong>M1</strong></td>
</tr>
<tr>
<td>No evidence of primary</td>
<td>No metastases to regional lymph</td>
<td>Distant metastases</td>
</tr>
<tr>
<td><strong>Tis</strong></td>
<td><strong>N1</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;0.5 mm, confined to mucosa</td>
<td>Metastases to regional lymph</td>
<td></td>
</tr>
<tr>
<td><strong>T1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamina propina or submucosa + ≤1 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscularis propina or submucosa + ≤1 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subserosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor invades visceral peritoneum or other organs/adjacent structures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Somatostatin Analog Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide SA</td>
<td>100-600 mcg/day SQ/IV in 2-4 divided doses for 2 weeks</td>
<td>Carcinoid</td>
</tr>
<tr>
<td>Octreotide LAR</td>
<td>Overlap with SA x 3-4 weeks, 20 mg IM at 4-week intervals for 2 months</td>
<td>Carcinoid</td>
</tr>
<tr>
<td>Octreotide LAR</td>
<td>30 mg injection every 28 days</td>
<td>Anti-proliferation</td>
</tr>
<tr>
<td>Lanreotide LAR</td>
<td>120 mg SQ injection every 4 weeks</td>
<td>Carcinoid &amp; Anti-proliferation</td>
</tr>
</tbody>
</table>
Telotristat for Carcinoid Diarrhea

• Approved in February 2017
  • Treatment for carcinoid symptom diarrhea
  • Refractory to SSA alone
  • Patients with metastatic NET

• 250 mg three times daily
  • In combination with SSA

• Cost (28 day supply)
  • $6196.80
## Comparison of the Baseline Demographics

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of Patients</th>
<th>Tumor Type</th>
<th>Tumor Prognosis</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
</table>
| PROMID  | 85                 | Midgut & Functional or Non-Functional | • Well-differentiated  
• Unknown progression | Locally inoperable NET, Karnofsky status >60% | Pretreatment with SSA >4 weeks,  
Pretreatment with IF-A, chemo, or chemoembolization |
| CLARINET| 204                | Pancreatic, Midgut, or Unknown & Non-Functional Only, SR+ | • Locally advanced or metastatic,  
• Low-grade  
• 96% had stable disease | Locally inoperable | Pretreatment with IF-A, chemo, or chemoembolization, radionuclide, or SSA, major surgery |

SR: Somatostatin Receptor
## Comparison of the Endpoints

<table>
<thead>
<tr>
<th>Trial</th>
<th>Interventions</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
<th>Common Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMID</td>
<td>Octreotide LAR 30 mg vs. Placebo</td>
<td>Time to tumor progression</td>
<td>Survival time and Tumor response</td>
<td>Gastrointestinal, Hematopoietic</td>
</tr>
<tr>
<td>CLARINET</td>
<td>Lanreotide 120 mg vs. Placebo</td>
<td>Progression-free survival</td>
<td>Overall survival, Quality of life, and Safety</td>
<td>Diarrhea, Abdominal Pain, N/V</td>
</tr>
</tbody>
</table>