Emerging Treatment Opportunities in Neuroendocrine Tumors (NETs)

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• Consulting
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  – Merrimack Pharmaceuticals

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  – Immune Design (unpaid)

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Outline

• Where have we been?
  – Brief overview of neuroendocrine tumors (NET)

• Where are we now?
  – Recent advances in diagnosis and imaging
  – Recent advances in systemic treatments for NET

• Where are we going?
  – Opportunities for research and better treatment options

Common assumptions about cancer

• The incidence of all cancers is decreasing

• The most common presenting symptom of cancer is pain

• When cancer has metastasized to other places in the body, survival is very short

• Treatment for metastatic cancer is chemotherapy only
  – And the treatment is toxic and ineffective
Nomenclature:
- Neuroendocrine Cancer
- Neuroendocrine Tumor (NET)
- Carcinoid

Neuroendocrine Tumors and Carcinoids

- Derived from stem cells with argentaffin and/or chromaffin properties

- Further characterization based on the expression of neuroendocrine markers:
  - neuron specific enolase (NSE)
  - chromogranins A, B, and C
  - synaptophysin

- Often secrete bioactive peptides such as serotonin, bradykinin, substance P, ACTH, gastrin, VIP, insulin, somatostatin, glucagon
US SEER data show a 5-fold increase in the past 30 years

Incidence of NETs is Rising Faster than Other Malignancies
NETs are a distinct group of tumors

- NETs are a group of malignancies that can arise from neuroendocrine cells throughout the body\(^1\)
  - NETs are characterized by their ability to secrete hormones and other peptides\(^1,2\)

Classification of NETs by anatomic site of origin

- **Foregut**
  - Nonfunctional
  - Functional
  - Gastrinoma
  - Insulinoma
  - Glucagonoma
  - VIPoma
  - Somatostatinoma

- **Midgut**
  - Jejunum
  - Ileum
  - Transverse, right colon
  - Appendix, rectum

- **Hindgut**
  - Left, sigmoid colon
  - Rectum


Origin of Carcinoid Tumors

Carcinoid Site

- Bronchopulmonary system: 28%
- Digestive system: 64%
- Other: 8%

Other:
- Colon, except the appendix: 2.3
- Appendix: 28
- Rectum: 28.5
- Duodenum: 4.6
- Jejunum: 2
- Ileum: 15
- NOS: 8%
- Other: 0.5

Where are we now?
Current Diagnosis and Treatment
Systematic Approach to Diagnosing NETs

History and physical exam
- Characteristic symptoms (dry flushing, cramps, nocturnal diarrhea)
  - Present in 8% to 35% of metastatic NETs\textsuperscript{1,2}

Special blood tests
- Chromogranin A (CgA)
- Urinary 5-hydroxyindoleacetic acid [(5-HIAA) (with presence of carcinoid syndrome]]
- Other biomarkers, including glucagon, gastrin

Scans
- Somatostatin-receptor scintigraphy (Octreoscan\textsuperscript{TM}, GA-68)
- Computerized tomography scan (CT)
- Endoscopic ultrasound (pancreatic-NET only)
- Positron emission tomography scans (PET)

Initial diagnosis of pancreatic NETs frequently occurs late in the disease

- Pancreatic NETs can often be challenging to diagnose
  - Symptoms are often nonspecific
  - Diagnosis is often delayed
- General pancreatic NETs classification

<table>
<thead>
<tr>
<th>Nonfunctional pancreatic NETs</th>
<th>Functional pancreatic NETs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not present with a syndrome associated with the hypersecretion of a hormone, although peptides are often released into the bloodstream</td>
<td>Typically present with a syndrome associated with the hypersecretion of a hormone</td>
</tr>
</tbody>
</table>


Early NET Symptoms Are Often Nonspecific and Generalized

- Telangiectasia (25%)
- Bronchoconstriction (3–19%)
- Abdominal pain (10–55%)
- Flushing (63–94%)
- Cardiac disease (14–41%)
- Cyanosis (18%)
- Diarrhea (68–84%)
- Dermatitis (5%)
- Arthritis (7%)
Constellation of Symptoms Can Make a Differential Diagnosis Difficult

Nonspecific Symptoms Are Common to Multiple Diagnoses

- Menopause
- Functional Bowel Disease
- Food Allergy
- Neurosis
- Asthma
- Thyrotoxicosis
- Alcoholism
- IBS
- Anxiety
- Peptic Ulcer

Symptoms
- Sweating
- Flushing
- Diarrhea
- Intermittent abdominal pain
- Bronchoconstriction
- GI bleeding
- Cardiac disease

Carcinoid syndrome

- Occurs in approximately 8% to 35% of patients with NET and occurs mostly in cases of patients with liver metastases

- Consequence of vasoactive peptides such as serotonin, histamine, or tachykinins released into the circulation

- Manifested by episodic flushing, wheezing, diarrhea, and, potentially, the eventual development of carcinoid heart disease
Nonspecific Symptoms Often Lead to a Delayed Diagnosis

- Presents to primary care
- Vague abdominal symptoms
- Referred to multiple specialists
- Symptoms become worse or patient consults for another reason
- Seen by gastroenterologist or other specialist who orders imaging
- A referral leads to a scan or patient scanned for another reason
- Surgeon, pathologist perform biopsy or resection
- Biopsy provides diagnosis of NET

Estimated time to diagnosis: 3 to 7 years

Special Laboratory Tests
Biomarkers

- Non-specific (All NETs)
  - Chromogranin A
  - Pancreatic polypeptide
  - Neuron specific enolase (NSE)
  - HCG

- Specific (individual syndromes)
  - 5-HIAA - glucagonoma
  - Insulin - VIP
  - Gastrin - others (SMS, ACTH, PTHrP, etc)

Foregut biomarkers

- Gastric NET
  - Fasting serum gastrin
  - Differentiate between types I & II (elevated gastrin) from type III (normal gastrin)
    - Type I: anti-parietal cell ab & anti-IF ab
    - Type II: ZES (elevated gastrin from ectopic secretion) Associated with MEN-1 syndrome
    - Type III: Sporadic. Normal gastrin
  - 5-HIAA is not useful in gastric NETs
Midgut biomarkers

- 5-HIAA 24-hour urine collection
  - Marker of choice for midgut carcinoid tumors
  - Sensitive (90%), but not specific (70%)
  - If elevated, marker is useful to assess response to treatment

- Serotonin:
  - less specific than 5-HIAA and no significant value is added to 5-HIAA level

- Neuron specific enolase:
  - less specific than chromogranin A

Urine 5-HIAA

Falsely elevated with certain foods or medications:

- Bananas
- Pineapple & Pineapple Juice
- Kiwi Fruit
- Nuts – Especially Walnuts & Pecans
- Avocados
- Tomatoes & All Tomato Products
- Eggplant
- Plums
- Guaifenesin expectorant
- L-Dopa
- Thorazine and Compazine
- Acetaminophen (Tylenol)
- Antihistamines
- MAO Inhibitors
- Muscle Relaxants (Robaxin, Valium and Flexeril)
Hindgut

• <1% of hindgut NETs produce a biomarker

• Routine analysis of serotonin or 5-HIAA are not recommended
  – Hindgut carcinoids rarely release 5-hydroxytryptamine and almost never cause elevation of the 5-HIAA

• Chromogranin A is useful in metastatic disease

Chromogranin A: A Valuable Diagnostic and Prognostic Tool

• Other conditions can cause increased Chromogranin-A levels and contribute to false positive results
  – Chronic gastritis, renal dysfunction, proton pump inhibitor therapy

• Chromogranin-A is used to monitor treatment response
  – Sensitive marker to monitor tumor progression

Anatomic Imaging: Need Triple Phase CT

Std

Arterial

Venous

Delayed

Delayed Washout

CT: computed tomography
Somatostatin Receptor: Tag and Target

Octreotide Scan

Locate NET in the body
Anatomic CT and Indium-111 Octreotide Scintigraphy

Diagnosis of NET with a Gallium-68 DOTATATE scan

Potential advantages:
- Higher sensitivity
- Possible change in management
- Shorter time to acquire images
- Lower radiation exposure

A) OctreoScan® 4 h after injection
B) PET 1 h after injection of 68Ga-DOTATATE in a patient with metastatic NET

Endoscopic Ultrasound

WHO Classification Groups NETs by Diagnostic Factors

<table>
<thead>
<tr>
<th>WHO classification</th>
<th>Well-differentiated neuroendocrine tumor(^1,^2)</th>
<th>Moderately differentiated neuroendocrine carcinoma(^1,^2)</th>
<th>Poorly differentiated neuroendocrine carcinoma(^1,^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological behavior</td>
<td>Low malignancy</td>
<td>Low malignancy</td>
<td>High malignancy</td>
</tr>
<tr>
<td>Mitotic Rate</td>
<td>&lt; 2</td>
<td>2-20</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Ki-67 index (%)</td>
<td>&lt; 3</td>
<td>3-20</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Infiltration, angioinvasion</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tumor size</td>
<td>≤ 2 cm</td>
<td>&gt;2 cm</td>
<td>&gt;3 cm(^a)</td>
</tr>
</tbody>
</table>

\(^a\)pancreatic NET

References:
Survival by Histology and Stage

Adapted from: Yao JC et al, JCO 2008

Treatment
What determines the treatment plan?

- Stage of the disease
  - Localized versus metastatic
- Grade of the tumor
  - Low versus high
- Burden of the tumor

Treatment Options

- Watchful Waiting
- Surgery
- Liver-directed therapy (for liver mets)
  - Hepatic artery embolization / Chemoembolization
  - Radiofrequency ablation
  - Cryoablation
- Systemic Therapy:
  - Octreotide
  - Targeted agents
  - 5FU, streptozocin, doxorubicin, etoposide, darcarbazine, temozolamide, gemcitabine, taxanes,
  - Poorly differentiated NET: cisplatin / etoposide
Surgical Resection: 
*Treatment of choice for early-stage disease*

Radiofrequency Ablation (RFA)

High frequency alternating current
↓
Ionic vibration & heat generation
↓
45°C: Protein denaturation
↓
70°C: Thermal coagulation
↓
100°C: Tissue desiccation

**Radiation Therapy:**
*Used sometimes to treat metastases*

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**Systemic Therapy Categories**

- Somatostatin analogs
  - Octreotide
  - Lanreotide (recently FDA approved)
- Peptide Receptor Radiotherapy (PRRT) – Pending FDA approval
- Anti-angiogenic Therapy
  - Bevacizumab
  - Sunitinib
- mTOR inhibition
  - Everolimus
- Cytotoxic Chemotherapy
  - Cisplatin-based regimens
  - Streptozocin regimens
  - Temozolomide regimens
Targeting NETs

- Somatostatin receptors highly expressed by NETs
  - Targeting SST receptors can provide symptom and disease control
- New targets could change treatment paradigm:
  - mTOR, PI3K, VEGF inhibitors
  - Other antiangiogenic agents
- High potential for combinations

Octreotide and Lanreotide

- Inhibitory hormone
  - Somatostatin
  - Somatotropin release-inhibiting factor (SRIF)
- Regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with somatostatin receptors and inhibition of the release of numerous secondary hormones
Octreotide for treatment of NET

SST Receptor

NET Cell

Improvement in symptoms

Normal Cell

PROMID: Octreotide LAR Slows Disease Progression in Midgut NETs

TTP in Midgut NET

Octreotide LAR vs placebo P < .001
HR: 0.34 (95% CI: 0.20–0.59)

- Octreotide LAR (n = 42)
  Median 14.3 months
- Placebo (n = 43)
  Median 6.0 months

Based on conservative ITT analysis

HR: hazard ratio; ITT: intent-to-treat; TTP: time to progression

Lanreotide for Metastatic NET

- 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)

Peptide receptor radionuclide therapy

- Somatostatin Receptor
- Radioactive Payload
- NET Cell
- Normal Cell
- NET tumor inhibition and destruction
**Octreotide scintigraphy**

Detects and localizes NETs and metastases and in patient follow-up to evaluate recurrence

Selection of patients with metastatic disease for peptide receptor radionuclide therapy (PRRT)

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**Progression-Free Survival**

N = 229 (ITT)
Number of events: 90

- $^{177}$Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio: 0.21
[0.129 – 0.338]
$p < 0.0001$

79% reduction in the risk of disease progression/death

Estimated Median PFS in the Lu-DOTATATE arm ≈ 40 month

All progressions centrally confirmed and independently reviewed for eligibility (SAP)

Strosberg et al. J Clin Oncol 23, 2016 (suppl 4S; abstr 194)
**Overall Survival (interim analysis)**

- N = 229 (ITT)
- Number of deaths: 35
  - 177Lu-Dotatate: 13
  - Octreotide 60 mg LAR: 22
- P = 0.0186

**Targeting Vascular Endothelial Growth Factor**
Sunitinib (Sutent)

Sunitinib Phase 3 Pancreas NET Study

Stopped early at unplanned time point
March 12, 2009

Islet cell w/PD over prior 12 months (340 planned, 171 accrued)

Sunitinib 37.5 mg continuous dosing

Placebo

Investigator-reported PFS:
11.4 mo with sunitinib vs 5.5 mo with placebo

PFS = progression-free survival
Raymond E et al. ASCO GI 2010; Abstract 127.
Targeting the mTOR/PI3K Pathway

RADIANT-4: Phase 3 Double-Blind, Placebo-Controlled Trial: Study Design

Patients with advanced non-functional NET N = 302
Stratified by:
• WHO PS
• Prior therapy

Primary endpoint: PFS (RECIST)
Secondary endpoints: Response, OS, biomarkers, safety, and PK

Everolimus 10 mg/d + BSC* n = 205
Crossover not allowed
Treatment until disease progression

Placebo + BSC* n = 97
Multi-phasic CT or MRI performed every 8-12 weeks

BSC: best supportive care; PS: performance status; WHO: World Health Organization
RADIANT-4: PFS by Investigator Review

Targeting the mTOR/PI3K and VEGF Pathway
Temsirilimus and Bevacizumab for Pancreas NET

Where are we going?
Opportunities for Research
Current Cancer Treatment Strategy:  
*One-size-fits-all*

We want to find the right drugs for the right patient!
BRAF inhibition in Melanoma


BRAF Inhibition in Melanoma

(Wagle et al. J Clin Oncol. 2011.)
PD-1 and PD-L1 Function as Immune Checkpoints: Prevents Activation

Clinical Activity of Anti-PD-1 Therapy: Melanoma

Baseline: April 13, 2012
April 9, 2013

72-yr-old male with symptomatic progression after bio-chemotherapy, HD IL-2, and ipilimumab
Clinical Activity of Anti-PD-1 Therapy: Lung Cancer

Lung cancer response to anti-PD-1 (4 prior treatments)


Pembrolizumab in patients with Merkel-Cell Carcinoma: rare form of NET

A

Viral Status (N=24)
Red Negative
Blue Positive

Percent Change in Sum of Longest Diameters of Target Lesions
-100 -75 -50 -20 0 20 50 75 100 125 150

B

Viral Status (N=24)
Red Negative
Blue Positive

Percent Change in Sum of Longest Diameters of Target Lesions
-100 -50 0 50 100

Months since Treatment Initiation

Patients with NETs need **multidisciplinary management** in a highly experienced cancer center

**Summary**

- The incidence of NETs is rising
- Diagnosis requires some additional specialized testing than what is typically required for most cancers
  - Have to think of the “zebra”
- Treatments continue to show better effectiveness and survival
  - Chemotherapy is rarely used for most NETs
- Research being performed will change the way we diagnosis and treat these cancers
  - Finding better targets and biomarkers
  - Immunotherapy?
Questions?