Neuroendocrine Cancer Updates

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Medical School Adage

“When you hear hoofbeats, think of horses, not zebras”

—Dr. Theodore Woodward, University of Maryland

Neuroendocrine Adage

“When you hear hoofbeats, think ZEBRAS, not horses” 🦓
Neuroendocrine Update

• Overview of Neuroendocrine Tumors
• Diagnosis of Neuroendocrine Tumors
• Treatment Options
• Symptom Management/Survivorship

Neuroendocrine Definition

• Tumors which arise from cells within the Endocrine System
• Typically sporadic, though can be inherited/genetic (MEN1 – some pancreas tumors, parathyroid, pituitary; MEN2 - medullary thyroid, pheochromocytoma, parathyroid)
• Biologically indolent
• Treatment and prognosis are dependent on anatomical site of origin, histology and size

Incidence and Prevalence

• 5-7 cases per 100,000
• 4-6 fold increase in the past 30 years
• Often delayed diagnosis ~ 5 years
• Most common: GEP-NETS(>50%)
• Least common: Thyroid, parathyroid, adrenal, pituitary
• Best Prognosis: rectal, appendiceal
• Worst Prognosis: colon, stomach – though improving d/t earlier diagnosis
• Common Metastatic Sites: liver, lymph nodes
• 5-10% have liver mets at diagnosis

Jones, Shah, Bloomston, 2012
Clinical Presentation/Diagnosis

- Tumor Cell of Origin
- Functional vs. Nonfunctional
- Bioactive Substances

**Functional vs. Nonfunctional**

- Functional secrete hormones causing symptoms, end organ damage
- Examples:
  - Carcioid: flushing, diarrhea, cardiac valvular fibrosis, bronchoconstriction
  - Pheo: hypertensive crisis
  - Insulinoma: hypoglycemia
  - Glucagonoma: hyperglycemia
  - Gastrinoma (ZES): ulcers
**NET Case Study**

65 year old female awoke with severe abdominal pain and presents to her local ED for treatment at 4 AM.

- **ROS:** The pain comes in waves, cramping and intermittent, lasting a few minutes, associated with nausea, loss of appetite, diarrhea stools, denies fever, chills but describes ‘hot flashes’ though is postmenopausal, denies weight loss or weight gain. Pain currently 7/10.
- **Physical Exam:** Abdomen distended, hypoactive bowel sounds noted in lower quadrants, diffuse tenderness to central abdomen with guarding noted, no rebound, no masses.
- **PMH:** GERD, HTN, Hyperlipidemia, CAD
- **PSH:** TAH 25 years ago, benign colon polyp removed in 2009 during colonoscopy. Tonsillectomy as a child.

**Clinical Evaluation**

- Labs were completed: CBC and CMP
  - Slightly elevated WBC count 12,000
- Abdominal X-ray notes her stomach is filled with fluid, and a distended small bowel.
  - Consistent with possible small bowel obstruction

- CT of Abdomen/Pelvis with contrast was then completed to confirm the diagnosis.
  - Partial obstruction confirmed and also noted liver lesions.

**Diagnosis of NET’s**

- **Radiological Imaging**
  - Computed Tomography
    - Tumor size, location, and metastases
  - Magnetic Resonance Imaging
    - Tumor size, location, mets
  - FDG-Positron Emission Tomography Scans
    - Detects cancer, mets
  - Somatostatin Analogue Scintigraphy (Octreoscan)
    - Tumor activity, size, location, mets
Diagnostic Localization Studies

- **Upper Gastrointestinal Endoscopy**
  - Stomach

- **Colonoscopy**
  - Terminal ileum
  - Colon
  - Rectum

- **Capsule Endoscopy**
  - Small bowel

- **Endoscopic Ultrasound**
  - Stomach
  - Duodenum
  - Pancreas
  - Rectum

- **Flexible Bronchoscopy**
  - Trachea
  - Proximal airways
  - Segmental airways

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Signs & Symptoms

- Stomach
  - Pain
  - Bleeding
  - Asymptomatic

- Small Intestine
  - Pain
  - Weight Loss
  - Asymptomatic

- Appendix
  - Asymptomatic
  - Cough
  - Hemoptysis

- GEP-NET’s
  - Pain
  - Obstruction
  - Carcinoid Syndrome

- Pancreas
  - Asymptomatic
  - Pain
  - Carcinoid Syndrome

- Lungs
  - Asymptomatic

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Clinical Presentation

Which of the following symptoms would be most indicative of a patient presenting with possible NET?

A. Fever, chills, and weight loss
B. Painful urination with increased frequency
C. Watery diarrhea, nausea, vomiting, and crampy abdominal pain, flushing
D. Pain in middle of abdomen, radiates to the back, may be relieved by changing position
Diagnosis: Biomarkers

- Plasma Chromogranin A
- 5-Hydroxyindoleacetic Acid
- Serotonin
- Histamine
- Gastrin
- Glucagon
- Vasoactive Intestinal Peptide
- Pancreatic Polypeptide
- Pancreastatin
- Somatostatin
- Bradykinin
- Substance P
- Neurotensin
- Human Chorionic Gonadotropin
- Neuropeptide K
- Neuropeptide L

Diagnosis: Classification/Grade

- Pathology/ Histology – obtain tissue
  - Fine Needle Aspiration
    - Samples of free cells and tissue fragments
  - Core Biopsy
    - Preserves tissue architecture
  - Incisional Biopsy
    - Removal of part of the lesion
  - Excisional Biopsy
    - Removal of entire lesion
  - Surgical Resection
    - Removal of entire diseased area or multiple organs

Classification of NET’s

- Well Differentiated Tumors
- Moderately Differentiated Carcinomas
- Poorly Differentiated Carcinomas
- Low Grade
- Intermediate Grade
- High Grade
**Histology Grades and Survival**

*Survival is impacted by primary site, grade, stage, and treatment for each NET

- **G1 = Ki-67 index <3%, < 2 mitosis/10 HPF**
  - Well-differentiated = 21% of cases
    - Median Survival = 124 months*

- **G2 = Ki-67 index 3-20%**
  - Moderately differentiated = 30% of cases
    - Present with synchronous distant metastases
    - Median Survival = 64 months*

- **G3/G4 = Ki-67 index >20%**
  - Poorly or Undifferentiated = 49% of cases
    - Present with synchronous distant metastasis
    - Median Survival = 10 months*

**Goals of Treatment**

- Curative vs Palliative Care
- Initiation of Treatment
  - Based on tumor burden or symptoms
- Treatment Options
  - Systemic therapy, Surgery/Interventional
  - Lack of consensus re: how to treat liver mets
- Patient Needs
  - Education, Symptom Management, QOL

**Treatment Options**

- **Surgical**
  - Resection
  - Transplant
  - Ablation, Perfusion
- **Radiation**
  - SIRT
  - MAB
- **Medical**
  - Somatostatin Analogs
  - Chemohepatology
  - Biologics
  - Clinical Trials
- **Interventional**
  - TACE, TAE
  - Ablation
Medical Options

Somatostatin Analogs:

**SANDOSTATIN (OCTREOTIDE)**
**LANREOTIDE (SOMATULINE DEPOT)**
- **How does it work?** Blocks receptors & inhibits production of tumor-producing hormones
- **When do we give these injections?**
  - carcinoid syndrome
  - prevention of carcinoid crisis
  - disease stabilization

Sandostatin (octreotide)

- **How is it given?**
  - Subcutaneous - test dose 1-2 weeks prior to starting LAR
  - Intramuscular (deep gluteal) - LAR, proper mixing needed, usually given every 4 weeks - 10mg, 20mg, 30mg
  - Intravenous - prevention of carcinoid crisis
- **What side effects may occur?**
  - Injection site pain, fatigue, hyperglycemia, hypoglycemia, hypothyroid, gallstones, sludge
  - Overall well tolerated, but costly
  - Sandostatin LAR may decrease diarrhea in approximately 60% of cases and flushing in 84% of cases

Somatostatin Analog

- **“PROMID” Study** Placebo controlled, double-blind, prospective study. Randomized study on the effect of Octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine Midgut tumors.
  - Decreased tumor progression (66%)
  - Arrested tumor growth (69%)
  - Improved carcinoid symptoms (flushing, diarrhea)
  - Rinke et al., 2009
- **Alpha Interferon** — may up-regulate somatostatin receptors, so it may be useful in combination therapy, but studies have had mixed reviews to date, and side effect profile is undesirable.
  - Close monitoring is required when using octreotide with insulinomas as it can lower blood glucose levels.
Lanreotide (Somatuline Depot)
- Phase 3 trial “CLARINET” - conducted over 2 yrs showed significant reduction of the risk of disease progression or death by 53% vs. placebo
  - Newly approved 12/2014 for treatment of unresectable, well- or moderately differentiated NET
  - Available in 60mg, 90mg, or 120mg recommended for NET pts
  - Given deep SC every 28 days in the superior external quadrant of the buttocks, no reconstitution required
  - Side effects include diarrhea, abdominal pain, HA, gallstones, flatulence, site pain, N/V, hyperglycemia

Chemotherapy – Systemic Treatment Options
- Who is treated with chemotherapy?
  - Poorly differentiated neuroendocrine patients
    - platinum-based therapy (Cisplatin/Etoposide or CAV) - cycle = 3 weeks
  - Advanced disease with well/moderately differentiated NET patients
    - Temodar (temozolomide)/Xeloda (capcetabine) - listed in NCCN guidelines

Chemotherapy
- Temodar/Xeloda - 70% radiographic response rate in patients with PNETs & 77% major biochemical response
  - Studies showing effective regimen in advanced NET - 28 pts with various types of NETs started treatment, 95% benefitted from the tx - 43% tumor shinkage & 54% delayed tumor growth
  - 28 day cycle - 2 weeks on, 2 weeks off
  - Xeloda - Days 1-14, BID dosing
  - Temodar - Days 10-14, given at night with Zofran 1 hr. prior
  - Side effects - diarrhea, hand/foot syndrome, fatigue, cytopenias, nausea/vomiting
  - Monitoring - phone calls, labs weekly, MD appt. monthly
### Biologics – Systemic Treatment Options

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Usual dose</th>
<th>How taken</th>
<th>Drug Class</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afinitor (everolimus)</td>
<td>5, 7.5, 10mg daily</td>
<td>10mg daily</td>
<td>with or without food</td>
<td>mTOR inhibitor</td>
<td>Mouth sores, fatigue, hyperglycemia, hyperlipidemia, cytopenias, infections</td>
</tr>
<tr>
<td>Sutent (sunitinib)</td>
<td>12.5, 15, 25mg daily</td>
<td>27.5mg daily</td>
<td>with or without food</td>
<td>TKI (VEGF)</td>
<td>Fatigue, HTN, diarrhea, N/V, cytopenias</td>
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<tr>
<td>Temodar (temozolomide)</td>
<td>300mg/m2 Qhs days 10-14 of 28 day cycle</td>
<td>1-2 hrs after eating</td>
<td>Alkylating agent</td>
<td>Fatigue, N/V, dysphagia, oral mucositis, alopecia</td>
<td></td>
</tr>
<tr>
<td>Xeloda (capecitabine)</td>
<td>1500mg/ m2 BID days 1-14 of 28 day cycle</td>
<td>With food &amp; water</td>
<td>Anti-metabolite</td>
<td>Diarrhea, hand/foot syndrome, fatigue</td>
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</tr>
<tr>
<td>Votrient (pazopanib)</td>
<td>200mg 800mg daily</td>
<td>1 hr before or 2hrs after eating</td>
<td>TKI (VEGF)</td>
<td>HTN, diarrhea, N/V, hair color changes, hand/foot syndrome, fatigue, hypoglycemia, infections</td>
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### Biologics

**When are patients offered these as treatment options?**

- Disease progression – take into consideration symptoms, tumor markers, and scan results = tailored treatment options from patient to patient
- Not eligible for clinical trials or have failed other trial options

**Other considerations for starting biologics:**

- Cost/insurance approval, patient availability to travel for appts every 2-4 weeks, patient psychosocial concerns

### mTOR Inhibitor

- **Afinitor (everolimus)**
  - Approved by FDA for pNET-HUGE ADVANCE!
  - Phase 2 & 3 clinical trials were conducted at The James
  - In the Phase 3 study, 400 patients with progressive pNET, when treated with everolimus had a median PFS of 11 months versus 4.6 months for patients treated with octreotide LAR alone
  - Common side effects – hyperglycemia, hyperlipidemia, cytopenias, fatigue, mouthsores
  - Hold drug for any infectious process
Tyrosine Kinase Inhibitors

- Sutent (sunitinib) and Nexavar (sorafenib)
  - Sutent - approved by FDA for treatment of PNET which was another huge advancement
  - Nexavar – off-label use as this drug is approved in advanced renal cell cancer
  - Common side effects – hypertension, diarrhea, hand/foot syndrome, fatigue, nausea, vomiting, mouthsores, hypothyroidism & hypophosphatemia
  - Close monitoring necessary with good patient/physician communication, dose modifications may be needed

Radiotherapy – PRRT

- Peptide Receptor Radionuclide Therapy is a systemic therapy with Yttrium 90 or Lutetium 177 labeled somatostatin receptor targeting peptides
  - Available in Germany, The Netherlands, Sweden, Switzerland, and clinical trial in Texas
  - Requirements for treatment: positive octreoscan, unresectable metastatic disease
  - Limitations of PRRT:
    - cost ranges from $10,000-$18,000/tx
    - insurance – unlikely to approve, payment required on arrival
    - travel expense with multiple return visits
    - Treatment is effective & results in tumor remission in high percentage of patients
    - Serious side effects rare

Clinical Trials

- Open trials at OSU for advanced NET:
  - ECOG-E2211 A Randomized Phase II Study of Temozolomide or Temozolomide and Capecitabine in Patients with Advanced Pancreatic Neuroendocrine Tumors
  - ALLIANCE-A021202 Prospective Randomized Phase II Trial of Pazopanib versus Placebo in Patients with Progressive Carcinoid Tumors
  - E2212 A Randomized, Double-Blinded, Placebo-Controlled Phase II Study of Adjuvant Everolimus Following the Resection of Metastatic Pancreatic Neuroendocrine Tumors to the Liver (opening soon!)
Clinical Trials

- Offer clinical trial as option prior to other therapies to give cutting edge treatment option
- Considerations prior to initiating clinical trial:
  - Eligibility – progression, labs, comorbid conditions, prior therapy, ECOG-PS
  - Travel for patient & availability for the trial
  - Insurance – Pre-determination done

Surgical Options: Resection

- Incidental Resection (appy)
- Typically well- or mod differentiated
- Curative Resection
  - Solitary, localized, or low volume disease
  - 60 - 98% 5 yr survival
  - < 20% are candidates
- Obstructing/Compressing Lesion
- Debulking of Liver Lesions (resection and/or ablation)
  - Only beneficial if 90% are resected
- Isolated Liver Perfusion
  - 50% overall response
- Liver Transplant
  - 36-47% 5 yr survival (less than other treatments)

Surgical/IR Options: Ablation

- Open, Laparoscopic, or Percutaneous
- Radiofrequency, Microwave, and Cryo
- Few lesions, < 3cm for best results
- 69-80% have relief of symptoms
- 10-35 month duration
Interventional Options

Hepatic Arterial Embolization
- Bland (HAE, TAE)
- Chemo (HACE, TACE)
- Radiation (Y90) (HAR, SIRT)

Goals:
- Decrease tumor burden
- Palliate symptoms
- Decrease hormone levels
- Average control ~ 2-3 years

Treatment Plan

Our patient’s symptoms have resolved, she reports mild abdominal discomfort, no N/V, formed BMs without problem - What should the next steps be for our patient?

A. Emergent Surgery > Somatostatin Analog > Systemic Chemotherapy
B. Immediate Systemic Chemotherapy > Hydration > Antidiarrheals
C. Stabilize > Somatostatin Analog > (Surgery) > Liver Directed Therapy
D. Best Supportive Care, Hospice

Symptom Management

- Flushing (94%)
- Diarrhea (78%)
- Heart valve lesions - Rt heart failure (53%)
- Cramping (51%)
- Telangiectasia (25%)
- Peripheral edema (19%)
- Wheezing (19%)
- Cyanosis (19%)

(represented GEP-NETs only)
Triggers: The 5 E’s

- Eating
- Ethanol
- Exercise
- Emotions
- Epinephrine

Carcinoid Syndrome

Heart
- Tachycardia
- Hypotension
- Valvular Disease

Liver
- Hepatomegaly

Gastrointestinal
- Diarrhea
- Cramps
- Nausea
- Vomiting

Skin
- Flushing
- Cyanosis

Respiratory
- Cough
- Wheezing
- Dyspnea

Retropertioneal & Pelvic
- Pain
- Local Fibrosis

Carcinoid Syndrome

- **Flushing** – Characterized by redness, warmth, tingling sensation on neck, face, chest, arms, etc. May last seconds to minutes, usually “dry”
  - Effective treatments:
    - Periactin (Cyproheptadine) - 4mg TID prn
    - Somatostatin analogs
    - Pepcid (Famotidine)

- Dietary teaching for triggers:
  - alcohol, caffeine, chocolate, tomato-based products, pineapple, nuts, high-fiber cereal, bread, dairy, spicy food, high fat food, vegetables, high sugar foods, and drinks
Carcinoid Syndrome

**Diarrhea** - need good assessment of consistency, frequency, color
- Consider if r/t surgery, bowel obstruction, recent travel, radiation to bowel area (non-carcinoid reason)
- Education on BRAT diet, proper use of antidiarrheals, avoiding foods known to cause diarrhea
- Try one antidiarrheal at a time
  - Immodium (loperamide), Lomotil (difenoxylate/atropine) often effective to help decrease frequency – take scheduled
  - Rare cases may require use of Codeine or Tincture of Opium
- Consistency may be improved with use of Colestid (cholestyramine)
- Steatorrhea type stool (oily, foamy, floaty with flatulence)
  - Pancreatic enzymes – Creon, Pancrelipase, Zenpep

Carcinoid Crisis

Typically Under High Stress situations, i.e., surgery, use of epinephrine in Novocaine

- **Cardiac Symptoms**
  - Extreme Blood Pressure Fluctuations
  - Arrhythmias
  - Flushing, Diaphoretic
- **Pulmonary Symptoms**
  - Wheezing or shortness of breath
- **Neurologic Symptoms**
  - Delirium, Confusion
- Give Sandostatin 200mcg SC 1 hr. prior to procedure
- May repeat 200mcg-500mcg SC every 1 hr. until drip prepared
- Give Sandostatin drip at 35mcg/hr. & then titrate

Pro-fibrotic Effects

Bioactive agents (serotonin, connective tissue growth factor) can cause fibrosis including:

- **Cardiac Fibrosis**: Right-sided heart valve damage, thickening of the right heart muscle (20% have at diagnosis)
- **Mesentary Fibrosis**: (intestinal carcinoid) – May cause bowel obstruction, mesenteric ischemia, intestinal perforation
- **Pulmonary Fibrosis**: May cause broncho-constriction, cyanosis, telangiectasis, red-to-purple flushing
Survivorship and Quality of Life

- **Long-term Physical Symptom Management**
  - Rare diagnosis, poorly understood disease
  - Fear and apprehension regarding treatment
  - Bothersome symptoms requiring coaching
  - Life-threatening disease

- **Psychosocial Support**
  - www.netpatientfoundation.com (UK)
  - www.caringforcarcinoid.org (USA)
  - www.virtualcancercentre.com (Australia)

- **Quality of Life Survey and Evaluation**
  - Distress Screening, EORT-QOL, EORT GI -NET Surveys
  - Advanced Care Planning, Patient Goals

Future Implications

- Increase physician and public awareness to aid in earlier diagnosis, increased support
- Care through multi-disciplinary teams
- Standardize classification, grading, and staging to ease research, clinical outcome comparison
- Additional clinical trials and access to treatment
- Improve symptom management and provide ongoing support
- Understand the natural history of the disease to improve long-term treatment and survivorship planning

Questions?