Carcinoid Tumors, Carcinoid Syndrome, and Pancreatic Neuroendocrine Tumors

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DISCLOSURES

Off-Label Usage
  • None

Interests
  • None
Most GEP-NETs are sporadic

Some familial syndromes produce GEPNETs:

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN1</td>
<td>MEN1</td>
<td>PNETs</td>
</tr>
<tr>
<td>VHL</td>
<td>VHL</td>
<td>PNETs</td>
</tr>
<tr>
<td>TSC</td>
<td>TSC-1, TSC-2</td>
<td>PNETs</td>
</tr>
<tr>
<td>VR-NF</td>
<td>NF-1</td>
<td>PNETs, carcinoid</td>
</tr>
</tbody>
</table>

Inactivating mutations lead to syndrome
• Inactivating mutations (occasionally deletions) of the *MEN1* gene on 11q13 give rise to the MEN1 syndrome
• PNETs arise in 60-70% or MEN1 patients
• 10% of PNETs are associated with MEN1
• LOH at 11q13 is common in PNETs
  – 80% of MEN1-associated PNETS
  – 68% of sporadic PNETs
**TSC1/TSC2 and NF-1**

- Inactivated in TSC and VR-NF
- Wild types act as repressors of mTOR
  - Regulatory gene in PI3K pathway
  - Controls proliferation downstream of growth factors
- mTOR may be a target for therapy in PNET
Carcinoid Tumors

- Clinically an uncommon tumor
  - Clinical incidence 1.9 per 100,000 (SEER 1992-1999, but incidence rising rapidly)
  - Autopsy incidence 650 per 100,000
- Majority originate in GI tract
- Many produce bioactive amines
- Most clinically significant carcinoids originate in the midgut
CARCINOID TUMOR
оригин AND HISTOLOGY

• Arise from neuroendocrine cells
• Stain for NSE, chromogranin, synaptophosphin
• Neurosecretory granules on EM
• Histology cannot:
  – Distinguish site of origin of tumor
  – Predict clinical behavior of a typical carcinoid
<table>
<thead>
<tr>
<th>SITE</th>
<th>METASTASIZE</th>
<th>SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>20-25%</td>
<td>(10% ACTH)</td>
</tr>
<tr>
<td>Stomach</td>
<td>20-30%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&gt;50%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Appendix</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Rectum</td>
<td>10%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
APPENDICEAL CARCINOIDS

- Usually asymptomatic incidental finding
- About 1/250 appendectomies
- For lesions <1 cm:
  - Simple appendectomy
  - No cancer surgery
  - No follow-up necessary
- Mayo retrospective review:
  - 108 cases <1 cm with simple appendectomy
  - No recurrences
SMALL BOWEL CARCINOIDs

- Most common in terminal ileum
- The most clinically significant carcinoids
- Even small lesions can metastasize
- May remain subclinical for long periods
  - May not present until metastatic (carcinoid syndrome)
  - Pain is most common local presentation
  - Mesenteric fibrosis (high local serotonin) and buckling
  - Occasional mesenteric ischemia
- Surgical resection
RECTAL CARCINOIDS

- May also present as small incidental lesions
- 1/2500 endoscopies
- Lesions <1 cm almost never spread
  - Simple excision is adequate
- Lesions >2 cm can be aggressive
  - Usually LAR or APR
  - But survival benefit not proven
GASTRIC CARCINOIDS

- 75-80% Reactive to hypergastrinemia (gastrin is trophic to enterochromaffin cells)
  - Atrophic gastritis or PA (Type 1)
    - Usually indolent for a long period
    - Antrectomy
    - Octreotide
  - Zollinger-Ellison (Type 2)

- Sporadic carcinoids (20%, Type 3)
  - Aggressive, similar to small bowel
CARCINOID SYNDROME

• “This witch’s brew of unlikely signs and symptoms, intriguing to the most fastidious connoisseur of clinical esoterica -”

• “The skin underwent rapid and extreme changes - resembling in clinical miniature the fickle phantasmagoria of the aurora borealis.”

  — William Bean, Circulation 1955; 12:1
CARCINOID SYNDROME

- Carcinoids secrete bioactive amines and hormones (APUDomas)
- Serotonin is the mediator most frequently responsible for the carcinoid syndrome
- Symptoms: diarrhea, flushing, others
- Long-term complications: cardiac valvular disease, ileus, retroperitoneal fibrosis
CLINICAL MANIFESTATIONS

- Diarrhea  73%
- Flushing   65%
- Asthma/wheezing  8%
- Pellagra  2%
- None      12%

Moertel. JCO 1987; 5:1503
CARCINOID SYNDROME

- Serotonin is almost 100% metabolized on the first pass through the liver.
- Primary carcinoids of midgut do **not** lead to carcinoid syndrome until metastatic.
- Once venous drainage bypasses the liver, serotonin can reach the target organs, giving rise to **carcinoid syndrome**.
CARCINOID HEART DISEASE

• Fibrous endocardial thickening or plaque
• A consequence of extended high serotonin levels
• Right-sided manifestations more common:
  – Tricuspid regurgitation
  – Pulmonic stenosis
• Prevented by controlling serotonin level
• Advanced cases may require valve replacement
TREATMENT OPTIONS FOR CARCINOID SYNDROME

• Hepatic-directed therapy
  – Surgical resection
  – Thermal ablation
  – Chemoembolization
  – Radioembolization

• Block serotonin secretion or activity
  – Somatostatin analogs

• Systemic therapy
  – Somatostatin analogs
  – Targeted therapy
  – Chemotherapy
• A naturally-occurring GI hormone which downregulates the release of other GI hormones, including serotonin
• It would be potentially useful to treat or prevent symptoms of carcinoid syndrome
• But serum half-life is only 3 minutes
OCTREOTIDE

• Synthetic analog of native somatostatin
• Similar activity to somatostatin, binds to hSSTR2, 3, and 5
• Much longer serum half-life (113 minutes)
• Requires parenteral administration
• Has become standard therapy for symptomatic relief of carcinoid syndrome
• Long-acting depot (IM) formulation
MARKERS FOR CARCINOID

• Serum serotonin is NOT useful
  – Paroxysmal secretion – wide diurnal variation

• Serum chromogranin
  – Stable serum levels
  – Not metabolized in first pass through liver
  – Useful in all neuroendocrine cancers

• 24-hour urinary 5HIAA
  – Integrated measure of circulating serotonin
  – Normal <6 mg/24 hrs
  – Dietary restrictions
CARCINOID CRISIS

- Precipitated by crisis or stress
  - Anesthesia, procedures
- Profound hypotension
  - Occasionally hypertension
- Severe flushing
- Bronchospasm
- Can be life-threatening
- Prophylactic octreotide
PANCREATIC NEUROENDOCRINE TUMORS

- Clinical PNETs even rarer than carcinoids, 1-1.5 per 100,000 (about 500/year)
- Seen in 0.15% of random autopsies
- May have a variety of hormonal activity:
  - Gastrin  Zollinger-Ellison
  - Insulin  Hypoglycemia
  - VIP  Pancreatic cholera
  - Glucagon  Necrotizing migratory erythema
  - Somatostatin  Diabetes, diarrhea, gallstones
- Commonly, may be hormonally inactive
PNET DIAGNOSIS

• Computed Tomography
  – Some active PNETs too small
• Magnetic Resonance Imaging
• Endoscopic Ultrasound (best resolution)
• Octreoscan
• F-DOPA PET (most sensitive)
• Venous sampling
OCTREOSCAN
METASTATIC DISEASE

- Hepatic-directed therapy
  - Radiofrequency ablation
  - Surgery
  - Chemoembolization
  - Radioembolization
- Chemotherapy
- Targeted therapy
  - Somatostatin analogs
  - m-TOR inhibitors
  - Sunitinib and other TKIs
- Radiotherapy
RF ABLATION

Electrode tines spread out within the tumor.

Electrode tines deliver radiofrequency energy to the tumor.
RF ABLATION FOR HEPATIC METASTASES FROM NEUROENDOCRINE TUMORS

- Cleveland Clinic experience
- 34 Patients, all neuroendocrine, 234 lesions
- 5% Morbidity, no mortality
- Complete symptom control 80%, partial 95%
- Median followup 1.6 years (1.0-5.4)
  - 59% Without hepatic progression
  - 41% New or progressive liver lesions
  - 25% New extrahepatic disease
  - 27% Died
- Median survival after ablation 1.6 years
CHEMОСEMBOLIZATION

- Lipiodol/Cisplatin/Doxorubicin/MMC
- 44 Patients, all neuroendocrine
- 5-year survival 50%
- Acceptable toxicity
  - Pain, fever, elevated liver enzymes
  - 25% grade 3
  - 1.4% 30-day mortality

Ruutiainen et al, J Vasc Interv Radiol 2007; 18:847
• Yttrium-90 microspheres  
  – Beta emitter, 50-day half-life

• Review of 148 refractory patients  
  – Objective response 63%  
  – Median survival 70 mos.

Kennedy et al, Am J Clin Oncol Cancer Trials 2008; 31:271
### Antiproliferative Activity of Interferon in Carcinoid

<table>
<thead>
<tr>
<th>Series</th>
<th>Patients</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Öberg (1986)</td>
<td>36</td>
<td>11%</td>
</tr>
<tr>
<td>Moertel (1989)</td>
<td>27</td>
<td>20%</td>
</tr>
<tr>
<td>Bajetta (1993)</td>
<td>34</td>
<td>12%</td>
</tr>
<tr>
<td>Saltz (1994)</td>
<td>14</td>
<td>7%</td>
</tr>
<tr>
<td>Faiss (2003)</td>
<td>27</td>
<td>4%</td>
</tr>
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**SOMATOSTATIN ANALOGS: CONTROL OF PROLIFERATION**

- Anecdotal reports of (infrequent) objective tumor response to somatostatin analogs
- Increased median survival with metastatic carcinoid since introduction of SSAs\(^1\)
  - 1980-91  24 months
  - 1992-97  48 months
- Antiproliferative effects were quantitated in a prospective trial completed in 2009

\(^1\)Quaedvlieg et al, Ann Oncol 2001; 12:1295
ANTIPROLIFERATIVE ACTIVITY OF OCTREOTIDE

- Prospective randomized trial of octreotide LAR in metastatic midgut carcinoids
- Highly significant increase in PFS
  - Placebo 6 months
  - Octreotide 14.3 months
  - $p=0.000072$

- Rinke et al, J Clin Oncol 2009; 27:4656
ANTIPROLIFERATIVE ACTIVITY OF OCTREOTIDE

- Carcinoid cells express five different receptors for somatostatin, hSSTR1-5
- Binding to hSSTR3 induces p53 and apoptosis
- Binding to others induces Rb and G1 arrest
- Octreotide binds avidly to hSSTR2, less avidly to hSSTR5 and, considerably less avidly, to hSSTR3
- Not all GEP-NETS express hSSTR3.
# SOMATOSTATIN RECEPTORS

<table>
<thead>
<tr>
<th>Receptor</th>
<th>hSSTR1</th>
<th>hSSTR2</th>
<th>hSSTR3</th>
<th>hSSTR4</th>
<th>hSSTR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cycle arrest</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Binding affinity (IC$_{50}$, nM):**

- Somatostatin: 2.26, 0.23, 1.43, 1.77, 0.88
- Octreotide: 1140, 0.56, 34, 7030, 7
- Lanreotide: 2230, 0.76, 107, 2100, 5.3

Grozinsky-Glassberg, Endocrine-Related Cancer Res 2009; 27:4656
**m-TOR INHIBITION**

- **Everolimus in PNETs**
  - Phase III trial in 410 progressing patients
  - PFS 11.0 mos. vs 4.6 mos. for placebo (p<.001)
  - 5% objective response rate
  - No difference in survival (73% of placebo patients crossed over), median not reached.

SUNITINIB

• Phase III trial in PNETs\(^1\)
  – 171 patients randomized to sunitinib vs placebo
  – Discontinued because of clear PFS advantage
  – PFS 11.4 mos. vs 5.5 mos.
  – Objective response 9.3%

• Phase II trial in PNETs and carcinoid\(^2\)
  – ORR 16.7% in PNET, 2.4% in carcinoid
  – PFS 10.2 mos in PNET, 7.7 mos. in carcinoid

\(^1\)New Engl J Med 2011; 364:501
\(^2\)JCO 2008; 26:3403
## SINGLE-AGENT CHEMOTHERAPY

<table>
<thead>
<tr>
<th></th>
<th>PNET</th>
<th>Carcinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptozocerin</td>
<td>36%</td>
<td>30%</td>
</tr>
<tr>
<td>5FU</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>20%</td>
<td>21%</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>33%</td>
<td>16%</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>8%</td>
<td>16%</td>
</tr>
</tbody>
</table>
COMBINATION CHEMOTHERAPY

- PNETs thought relatively chemosensitive
- Combinations studied in PNETs:
  - STZ-DOX 69%* (18 month survival)
  - STZ-5FU 45%* (14 month survival)
  - FAS 39% (37 month survival)
  - CAP/TEM 70% (PFS 18 mos, 92% 2-yr surv.)
- One report of lower activity for STZ-DOX
  - Only 1 response in 16 consecutive patients
- Carcinoid significantly less chemosensitive

*Did not use RECIST criteria
CAPECITABINE/TEMOZOLOMIDE

• Four-week cycles:
  – Capecitabine 750 mg/m2 q12h days 1-14
  – Temozolomide 200 mg/m2 qd days 10-14

• First-line PNETs (30 patients)\(^1\)
  – CR+PR 70%
  – PFS 18 mos.
  – 2-yr survival 92%

• Refractory GEP-NETs (18 patients)\(^2\)
  – CR+PR 61% (one path CR in carcinoid)
  – PFS 14 mos.
  – OS 83 mos.

1. Strosberg et al, Cancer 2011; 117:268
RADIOTHERAPY

- Carcinoid is a radiosensitive tumor
- Two reports of 54-55% objective response to RT$^{1,2}$
- Anecdotal report of long-term survivors after total abdominal irradiation$^3$
- Radiation usually controls osseous metastases
  - 1. Schupak, IJROBP 1991; 20:489
  - 3. Gaitan-Gaitan, IJROBP 1975; 1-9
A MANAGEMENT STRATEGY

- Hepatic resection if possible with curative intent
- Hepatic-directed therapy (surgery, thermal ablation, chemoembolization, radioembolization) if major debulking will result
- Somatostatin analog for all patients with residual disease
- Further selected therapy on progression