Carcinoid and Pancreatic Neuroendocrine Tumors

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NET: Overview

• Thought to arise from cells in the diffuse neuroendocrine system throughout the body

• May pursue more indolent clinical course than other malignancies

• Ability to secrete peptides that may result in characteristic symptoms of hormone hypersecretion
Neuroendocrine Tumors: Incidence and Prevalence

- Early estimates of incidence 1-2 per 100,000 population\(^1\)
- Diagnosed incidence increasing, likely due to improved awareness, classification, and diagnostic modalities\(^2\)
- Prevalence estimated to be >100,000 in United States

Cases selected from SEER database (1973 to 2004) using International Classification of Disease for Oncology histology codes 8150 to 8157, 8240 to 8246, and 8249.

1. Modlin et al, Cancer 2003; 97: 934-59
### Neuroendocrine Tumors: Histologic Classification

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Grade</th>
<th>Mitotic count*</th>
<th>KI-67 index</th>
<th>ENETS, WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>Low (G1)</td>
<td>&lt; 2 per 10 HPF</td>
<td>≤ 2%</td>
<td>Neuroendocrine Tumor, Grade 1</td>
</tr>
<tr>
<td></td>
<td>Intermediate (G2)</td>
<td>2 - 20 per 10 HPF</td>
<td>3 - 20%</td>
<td>Neuroendocrine Tumor, Grade 2</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>High (G3)</td>
<td>&gt;20 per 10 HPF</td>
<td>&gt;20%</td>
<td>Neuroendocrine Carcinoma, Grade 3, Small Cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neuroendocrine Carcinoma Grade 3, Large Cell</td>
</tr>
</tbody>
</table>
Pancreatic Neuroendocrine Tumors*  
(Islet cell tumors)

Carcinoid Tumors

*Pancreatic NET comprise 5-8% of all NET in SEER; 22-28% in institutional databases

2. Pape UF et al, Endocrine-Related Cancer 2008; 15: 1083-97
3. Ter-Minassian et al, Proc ASCO 2010
Pancreatic NET

- 30-40% associated with symptoms of hormone hypersecretion
- 60-70% “Non-functioning”

Necrolytic migratory erythema associated with glucagonoma

FIGURE 1. Tumor subtypes.

Strosberg et al, Pancreas 2009; 38: 255-258
Pancreatic NET: Management of Secretory Symptoms

- **Insulinoma**: Diet modifications, diazoxide, everolimus, +/- somatostatin analog
- **Glucagonoma**: Somatostatin analog, consider TPN
- **VIPoma**: Somatostatin analog
- **Gastrinoma**: PPIs, somatostatin analog
Pancreatic NET: Surgical Resection

- Enucleation, distal pancreatectomy, or Whipple depending on tumor size/ location
- Multiple neoplasms common in MEN-1
- Prognosis good when complete resection performed
Carcinoid Tumors

- **Foregut (33%)**: lungs and bronchi, stomach
- **Midgut (34%)**: small intestine, appendix, proximal large bowel
- **Hindgut (14%)**: distal large bowel, rectum
Bronchial Carcinoid Tumors

- Present with hemoptysis, cough, wheezing
- Common cause of Cushings syndrome due to ectopic ACTH (carcinoid syndrome rare)
- Prognosis correlates with histology: typical vs “atypical”
Gastric Carcinoid Tumors

- Three types of gastric carcinoids:
  - Type I: associated with chronic atrophic gastritis type A (CAG-A)
  - Type II: associated with Zollinger-Ellison syndrome and MEN-1
  - Type III: sporadic gastric carcinoids
Type I and Type 2 Carcinoids Are Associated With Hypergastrinemia

- Enterochromaffin-like Cell
- ECL-cell Hyperplasia
- Multiple Gastric Carcinoids
Sporadic Gastric Carcinoids

- Comprise 15%–20% of gastric carcinoids
- Usually solitary
- Usually greater than 1 cm in size
- Often invasive and metastatic at presentation
Appendiceal Carcinoids:

- Most commonly present as incidental finding with acute appendicitis; usually in younger individuals (30’s)

**Prevalence of Metastases According to Tumor Size**

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>0%</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–3 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Treatment Recommendations**

<table>
<thead>
<tr>
<th>Size</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 cm</td>
<td>Simple appendectomy</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>Octreoscan, right colectomy</td>
</tr>
</tbody>
</table>

## Rectal Carcinoids: Treatment Recommendations

<table>
<thead>
<tr>
<th>Size</th>
<th>Treatment</th>
<th>% Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 cm</td>
<td>Transanal or endoscopic excision, if possible</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>Octreoscan, CT, then LAR or APR</td>
<td>&gt;50%</td>
</tr>
</tbody>
</table>
Small Bowel Carcinoid

- Present at advanced stage due to difficulty in diagnosis
- Associated with intermittent obstruction/bowel ischemia.
- Resection recommended for symptoms even with metastatic disease

Hepatic metastases from carcinoid tumor

Primary Small Bowel Carcinoid
Metastatic Neuroendocrine Tumors: What are the Treatment Options?

- Somatostatin analogs
- Interferon
- Treatment of Liver Metastases
- Cytotoxic Chemotherapy
- “Targeted” Therapies
Carcinoid Syndrome

- Caused by secretion of serotonin and other neuropeptides into systemic circulation
- Manifested by episodic flushing, diarrhea, and eventual right sided valvular heart disease
- Treated with somatostatin analogs

Flushed skin associated with carcinoid syndrome

Carcinoid Heart Disease: Tricuspid valve is fibrotic and leaflets retracted
Antiproliferative Effect of Somatostatin Analogues and/or Interferon-α in Neuroendocrine Tumors

Placebo-Controlled Randomized Study of Octreotide LAR vs Placebo in Patients with Metastatic Neuroendocrine Midgut Tumors (PROMID)

85 Patients with locally inoperable or metastatic well differentiated midgut NET

Octreotide LAR 30 mg IM monthly

Median TTP: 14.3 mos
HR: 0.33; P=0.00037

Placebo
Median TTP: 6 mos

Arnold et al, 2009 Gastrointestinal Cancers Symposium A121
Dose Escalation Study of Pasireotide (Jen Chan MD, PI)

- Pasireotide targets multiple somatostatin receptor subtypes
- Dose escalation study to assess safety and preliminary efficacy
- Multiple dose cohorts (60mg, 80mg, 120 mg, 180 mg monthly)
Hepatic resection considered for limited hepatic metastases…

Hepatic artery embolization considered for patients with liver predominant disease that is not resectable

Overall survival is encouraging, but disease recurrence is common.

Figure 1. Survival after OLT for metastatic neuroendocrine tumors. NED = nonevidence of disease; AWD = alive with disease. Carcinoids vs. noncarcinoid apudomas; p < 0.001.

Figure 2. Disease-free survival after OLT for metastatic neuroendocrine tumors. Carcinoids vs. noncarcinoid apudomas; p < 0.001.

LeTreut, 1997
**Streptozocin/5FU vs Doxorubicin/5FU in Advanced Carcinoid (E 1281)**

249 Patients

**Streptozocin/5FU**
- PFS: 5.3 mos
- Response Rate: 16%
- Renal Toxicity: 34.5%

**Doxorubicin/5FU**
- PFS: 4.5 mos
- Response Rate: 15.9%

Sun et al, J Clin Oncol 2005; 23: 4897-4904
Streptozocin-based Therapy for Pancreatic NET

• Streptozocin approved for pancreatic NET in 1982
• Streptozocin/doxorubicin associated with progression free survival benefit compared to streptozocin/5-FU
• Response rates 30-40% in retrospective series
• Not commonly used due to toxicity concerns

## Temozolomide-Based Therapy in Pancreatic NET

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retrospective Series</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temozolomide&lt;sup&gt;1&lt;/sup&gt;</td>
<td>12</td>
<td>8%</td>
</tr>
<tr>
<td>Temozolomide/ Capecitabine&lt;sup&gt;2&lt;/sup&gt;</td>
<td>30</td>
<td>70%</td>
</tr>
<tr>
<td>Temozolomide (various regimens)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>53</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Prospective Trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temozolomide/ Thalidomide&lt;sup&gt;4&lt;/sup&gt;</td>
<td>11</td>
<td>45%</td>
</tr>
<tr>
<td>Temozolomide/ Everolimus&lt;sup&gt;5&lt;/sup&gt;</td>
<td>24</td>
<td>35%</td>
</tr>
<tr>
<td>Temozolomide/ Bevacizumab&lt;sup&gt;6&lt;/sup&gt;</td>
<td>15</td>
<td>33%</td>
</tr>
</tbody>
</table>

E2211: Randomized Phase II Study of Temozolomide + Capecitabine vs. Temozolomide Alone in Patients with Advanced Pancreatic NET

Status: Approved by NCI

**Primary Endpoint:** PFS

**Arm 1:** Temozolomide 200 mg/m²/day d 1-5 q 28 days

**Arm 2:** Temozolomide 200 mg/m²/day d10-14+ Capecitabine 1000 mg/m² d1-14 q 28 days
Immunohistochemical Tyrosine Kinase Expression in NET (Analysis of TMA)

% Tumors Expressing Marker

VEGF (Carcinoid)*

VEGFR (Carcinoid*)

*Courtesy John Glickman, MD PhD, BWH
Targeting the VEGF Pathway in Neuroendocrine Tumors

Angiogenesis and Tumor Growth

VEGF

VEGF Receptor

Bevacizumab

Sunitinib,
Sorafenib,
Pazopanib
Phase III, Randomized, Double-Blind Study of Sunitinib vs. Placebo in Patients with Advanced, Progressive, Well-Differentiated Pancreatic Neuroendocrine Tumors

**Key Eligibility Criteria**
- Well-differentiated, malignant pancreatic endocrine tumor
- Disease progression in past 12 months

**Randomization**
- Arm A: Sunitinib 37.5 mg/day orally, continuous daily dosing (CDD)*
- Arm B: Placebo*

**Primary endpoint:** PFS

After trial closure patients became candidates for open-label sunitinib in trial NCT00443534 or NCT00428220

Niccoli et al, Proc ASCO 2010 A 4000
Sunitinib in pNET: Investigator-Assessed Progression-Free Survival

Median PFS

Sunitinib 11.4 months (95% CI 7.4, 19.8)
Placebo 5.5 months (95% CI 3.6, 7.4)

HR=0.418 (95% CI 0.263, 0.662)
P=0.0001

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>86</td>
<td>39</td>
<td>19</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Placebo</td>
<td>85</td>
<td>28</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
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</table>
CALGB 81103: Randomized Phase II Study of Pazopanib or Placebo in Patients with Advanced Carcinoid

**STATUS: Approved by NCI**

**Require:**
- PD within 12 mos

**Stratify:**
- Concurrent octreotide
- PS

150 pts

**Arm 1:** Pazopanib 800 mg po qd

**Arm 2:** Placebo

Crossover at progression

Primary Endpoint: PFS
RADIANT-3: Everolimus vs. Placebo in Advanced Pancreatic NET

Patients with advanced pNET
n=410

Randomization Aug. 2007 – May. 2009

*concurrent somatostatin analogs allowed
Investigator-Assessed Progression-Free Survival

Kaplan Meier median PFS
Everolimus: 11.04 months
Placebo: 4.60 months

HR: 0.35 (95% CI [0.27, 0.45])
$p$-value: <0.0001

- $p$-value obtained from stratified one-sided log-rank test
- Hazard ratio is obtained from stratified unadjusted Cox model
RADIANT 2: Octreotide with or without Everolimus in Advanced Carcinoid

Patients with advanced carcinoid $n=429$

Randomization Dec 2006 – May 2008

Multi-phasic CT or MRI performed at baseline and every 12 weeks

Everolimus 10 mg/d + Octreotide LAR

Placebo + Octreotide LAR

Cross over

Treatment continued until progression

M. Pavel, Phase-III study shows everolimus delays tumor progression in hard-to-treat neuroendocrine tumors. ESMO. Milan Italy
RADIANT 2: PFS by Local Investigator Review

Kaplan-Meier median PFS
Everolimus + Octreotide LAR: 12.0 months
Placebo + Octreotide LAR: 8.6 months

Hazard ratio = 0.78; 95% CI [0.62–0.98]
P-value = 0.018

Total events = 284
Censoring times
E + O (n/N = 128/216)
P + O (n/N = 156/213)

No. of patients still at risk
E + O 216 199 167 129 119 100 81 74 68 62 51 40 32 24 18 11 4 2 1 0 0
P + O 213 201 159 121 114 92 75 72 64 56 50 41 27 21 11 10 4 1 0 0

• P-value is obtained from the one-sided log rank test
• Hazard ratio is obtained from unadjusted Cox model

E + O = Everolimus + Octreotide LAR
P + O = Placebo + Octreotide LAR
RADIANT 2: PFS by Central Review*

Kaplan-Meier median PFS
Everolimus + Octreotide LAR: 16.4 months
Placebo + Octreotide LAR: 11.3 months

Hazard ratio = 0.77; 95% CI [0.59–1.00]
\(P\)-value = 0.026

Total events = 223

No. of patients still at risk
E + O  216 202 167 129 120 102 81 69 63 56 50 42 33 22 17 11 4 1 1 1 0
P + O  213 202 155 117 106 84 72 65 57 50 42 35 24 18 11 9 3 1 0 0

* Independent adjudicated central review committee
\(P\)-value is obtained from the one-sided log rank test
Hazard ratio is obtained from unadjusted Cox model

E + O = Everolimus + Octreotide LAR
P + O = Placebo + Octreotide LAR
Exome Sequencing of Pancreatic NETs

Table 1. Comparison of commonly mutated genes in PanNETs and PDAC, based on 68 PanNETs and 114 PDACs.

<table>
<thead>
<tr>
<th>Genes</th>
<th>PanNET</th>
<th>PDAC †</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN1</td>
<td>44%</td>
<td>0%</td>
</tr>
<tr>
<td>DAXX, ATRX</td>
<td>43%</td>
<td>0%</td>
</tr>
<tr>
<td>Genes in mTOR pathway</td>
<td>15%</td>
<td>0.80%</td>
</tr>
<tr>
<td>TP53</td>
<td>3%</td>
<td>85%</td>
</tr>
<tr>
<td>KRAS</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>TGFBR1, SMAD3, SMAD4</td>
<td>0%</td>
<td>38%</td>
</tr>
</tbody>
</table>

*Includes point mutations and indels.
†Data from Jones et al., Science 321, 1801 (2008).

Jiao et al, Science 2011; 331: 1199-203
Expression of mTOR pathway components in NET

(ZR. Qian MD PhD)

PI3K p85

pAKT

mTOR and pmTOR

TSC2 (+ and -)

p4EBP1
Future Directions: Targeting the RTK/ PI3-K /mTOR Pathway in NET

Growth Factors:
- IGF-1
- PDGF
- VEGF

Growth Factor Receptors:
- IGF-1R
- VEGFR
- PDGFR
- RET

Targeted Agents:
- Bevacizumab
- AMG 479
- Sunitinib
- Pazopanib
- Sorafenib
- Everolimus
- Temsirolimus

Cell Growth & Survival

mTOR

AKT

PI3-K

Growth Factors & Receptors

mTOR

AKT

PI3-K

Targeted Agents

Everolimus
Temsirolimus
CALGB 80701: Randomized Phase II Study of Everolimus Alone or in Combination with Bevacizumab, in Patients with Advanced Pancreatic NET

Status: >40/138 patients accrued

**Primary Endpoint:** PFS

**Arm 1:** Everolimus 10 mg po qd + octreotide

**Arm 2:** Everolimus 10 mg po qd + Bevacizumab 10 mg/kg IV every 2 wks + octreotide
Everolimus and Pasireotide: Maximum % Reduction in Tumor Lesions

08-087 RAD001 and SOM230 in NET

Patients (N=21 evaluable patients)

* PD due to new lesions

(J. Chan, ASCO Gastrointestinal Cancers Symposium, 2010)
Randomized Phase II Study of Everolimus Alone or in Combination with Pasireotide, in Patients with Advanced Pancreatic NET

Status: >70/150 patients accrued

Arm 1: Everolimus 10 mg po qd

Arm 2: Everolimus 10 mg po qd + Pasireotide 60 mg IM q 28 days

Primary Endpoint: PFS
Peptide-Receptor Targeted Therapy

Hepatic metastases in NET patient imaged by OctreoScan
### Efficacy of Peptide Receptor Radiotherapy (PRRT) in Patients with Advanced Neuroendocrine Tumors

#### 177-Lu-DOTA (Retrospective Series)

<table>
<thead>
<tr>
<th>Tumor type</th>
<th># Pts</th>
<th>CR+PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>188</td>
<td>42</td>
</tr>
<tr>
<td>Non-functioning PET</td>
<td>72</td>
<td>31</td>
</tr>
<tr>
<td>Functioning PET</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Unknown origin</td>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>310</td>
<td>92 (30%)</td>
</tr>
</tbody>
</table>

#### 90-Y Edotretotide (Prospective Trial)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th># Pts</th>
<th>CR+PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>90</td>
<td>4 (4.4%)*</td>
</tr>
</tbody>
</table>

*Statistically significant improvement in self-reported symptoms was documented in evaluable pts

DJ Kwekkeboom et al, J Clin Oncol 2008; 26: 2124-2130

Carcinoid Xenografts and Cell Lines

CAR2 Primary

CAR2 Xenograft

H&E

Chromogranin A

CAR4 cell line

CAR8 cell line

Chromogranin A
NETS: Multiple Treatment Options

• **Somatostatin analogs** for symptoms (and in carcinoid for tumor) control

• **Hepatic directed therapies** for hepatic predominant disease

• **Alkylating agents** (streptozocin or temozolomide) are active in pancreatic NET

• **VEGF pathway** (Sunitinib) and mTOR inhibitors (Everolimus) improve PFS in advanced pancreatic NET; further studies in carcinoid anticipated

• **Future studies**: combination therapy, molecular and genetic predictors of response, novel targets and agents
Combining Compassionate Care with Cutting Edge Research for Neuroendocrine and Carcinoid Tumor Patients