Emerging Trends in Neuroendocrine Tumor Management

Shereen Ezzat, MD, FRCP(C), FACP

Head, Endocrine Site Group, Princess Margaret Cancer Centre
Senior Scientist, Ontario Cancer Institute
University of Toronto
Objectives

1) Diagnostic dilemmas:
   - Understand the features distinguishing slow-growing tumors from the aggressive endocrine carcinomas

2) Therapeutic conundrums:
   - Can novel effective therapy be based on underlying pathogenetic/progression factors?
Aims:

- Advances in classification of NETs
- Clinical Features
- Biomarkers
- Molecular imaging
- Today’s therapeutic landscape
Increasing Incidence of neuroendocrine tumors in the western world

5.0/100,000 inhabitants

Lung
Small intestine
Rectum

GEP-NET ~ 75%

Surveillance, Epidemiology and End Results (SEER), US population 1974-2005

Modlin et al., Lancet Oncol. 2008
Myth #2

- Neuroendocrine tumors (NETs) are not really cancers
Myth #3: 

- Neuroendocrine tumors are gut tumors resulting largely in flushing and diarrhea
<table>
<thead>
<tr>
<th>Hormone</th>
<th>Cell</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrin</td>
<td>G</td>
<td>ZE syndrome</td>
</tr>
<tr>
<td>Glucagon/GLP</td>
<td>A/L</td>
<td>DM/rash</td>
</tr>
<tr>
<td>Insulin</td>
<td>β</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>Secretin</td>
<td>S</td>
<td>WDHA</td>
</tr>
<tr>
<td>Serotonin</td>
<td>ED</td>
<td>“carcinoid”</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>D</td>
<td>DM/gallstone</td>
</tr>
<tr>
<td>VIP</td>
<td>?</td>
<td>VM syndrome</td>
</tr>
</tbody>
</table>
## Classification of GEP Endocrine Tumor Cells

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Cell</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecystokinin</td>
<td>I</td>
<td>?</td>
</tr>
<tr>
<td>Pancreatic polypeptide</td>
<td>PP</td>
<td>?</td>
</tr>
</tbody>
</table>
GEP-Neuroendocrine tumours

- Carcinoid (50%)
- Gastrinoma (20%)
- Insulinoma (15%)
- VIPoma (7%)
- Glucagonoma (5%)
- Other (3%)
Anatomic Distribution of GEP tumours

- appendix: 35%
- ileum: 20%
- stomach: 10%
- rectum: 10%
- duodenum: 5%
- bronchus: 10%
- colon: 5%
- other: 5%
“Carcinoid” or “Endocrine Carcinoma”

- ? well differentiated neuroendocrine tumors
- ? clinical “carcinoid syndrome”
- ? prognosis
Criteria of Malignancy in GEP Tumors

- Cytologic features
- DNA Ploidy
- Proliferation markers:
  - *Ki 67 or MiB1 labeling index
- Invasion
  - capsular, adjacent tissues, perineural, vascular
The Fundamental Elements to Targeting Cancer

- MEN1 mutations leading to attenuation of p18, p27 driving cell cycle
- Self-sufficiency in growth signals
- Evading apoptosis
- Sustained angiogenesis
- mTOR pathway activation leading to increased HIF activity
- Limitless replication
- DAXX/ATRX mutations leading to alternative lengthening of telomeres
- Insensitivity to antigrowth signals
- Tissue invasion and metastasis
- mTOR pathway activation
Gain or loss of genetic information
Cancer Susceptibility Genes

The diagram illustrates the relationship between relative risk and minor allele frequency for different cancer susceptibility genes. It shows:

- Rare to very rare, high-risk alleles found through family studies.
- Rare, moderate-risk alleles found through resequencing.
- Common, low-risk alleles found through genomewide association studies.

The genes mentioned include:

- TP53
- BRCA1
- BRCA2
- PTEN
- CDH1
- STK11
- BRIP1
- ATM
- PALB2
- CHEK2
- 6q
- TOX3
- 2q
- FGFR2
- MAP3K1
- 5p
- AKAP9
- 8q
- CASP8

The chart also highlights that too many low-risk alleles are hard to find.
Identifying Genetic Signatures in Cancers
DNA Microarray Analysis: GI Carcinoids and PNETs
Cluster independently

GI Carcinoid	PNET

Duerr et al. Endocr Rel Cancer. 2008
Benign and malignant PNETs cluster independently

- 112 genes differentially expressed with $P < 0.05$

- "benign" cluster
  - 3/3 WDETs – benign
  - 8/9 WDETs – LGM
  - 1/7 WDEC

- "malignant" cluster
  - 6/7 WDECs
  - 1/9 WDETs - LGM

Distinction between pNET and PDAC
Different Genes for Different Pancreatic Tumors

<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>

The table above shows the comparison of commonly mutated genes in PanNETs and PDACs. The mutations were based on 68 PanNETs and 114 PDACs. The data were sourced from Joneset et al. in Science 321, 1801 (2008).
Altered Telomers in DAXX/ATRX + pNETs

Science. 2011 Jul 22;333(6041):425
The Elusive Small Intestine NET Gene

Recurrent somatic mutations and deletions in CDKN1B, the cyclin-dependent kinase inhibitor gene, which encodes p27.

Frameshift mutations of CDKN1B in 14 of 180 SI-NETs
Hemizygous deletions encompassing CDKN1B in 7 out of 50 SI-NETs

Nominating p27 as a tumor suppressor and implicating cell cycle dysregulation in SI-NETs.

Nature Genetics; 2013:45,1483–1486.
Therapeutic Options NETs

- **Surgery**
  - Curative (rarely)
  - Ablative (very often)

- **Debulking**
  - Radiofrequency ablation (RFA)
  - Embolization/chemoembolization/radioembolization

- **Irradiation**
  - External (bone, brain-mets)
  - Tumor targeted
  - Radioactive therapy (MIBG, $^{90}$Y-DOTATOC, $^{177}$Lu-DOTATATE)

- **Medical therapy**
  - Chemotherapy
    - Biological treatment:
      - Somatostatin analogs
      - α-interferon
      - m-TOR inhibitors
      - VEGF R inhibitors
      - Other TKI:s
Factors influencing the therapeutic decision

- Type of NET-tumor
- TNM grade and stage
- Extent of liver involvement
- Functioning v.s. non-functioning tumor
- Patients performance status
- Availability of different therapeutic modalities
- Most patients will require a combination of surgery, PRRT and medical treatment
Translations of 7th edition planned
Impact of Distant Metastases on iNET Disease Outcomes

Arajuo P & Ezzat S. PloS One 2013
Impact of Octreo-scanning

Araujuo P & Ezzat S. PloS One 2013
Comparison of 2010 WHO Grading vs. AJCC Staging (7th Edition) in intestinal NETs

- Progression free survival (months)
- Overall survival (months)
- Death related to NET (months)
- Cumulative survival plots for WHO classification and AJCC stage

Statistical significance levels:
- p = 0.004
- p = 0.001
- p = 0.003
- p = 0.320
- p = 0.017
AJCC Staging and Octreotide therapy in Intestinal NET
WHO Grading Alone is Not Fully Informative During Therapy

- **WHO = G1**
- **WHO = G2**
- **AJCC = III**

**Progression-Free Survival (months)**

- **Cum Survival**
- **Octreotide use**
  - No
  - Yes
  - No-censored
  - Yes-censored
  - NS

**Overall Survival (months)**

- **Cum Survival**
- **Octreotide use**
  - No
  - Yes
  - No-censored
  - Yes-censored
  - NS
Pharmacologic Approaches
Cellular Sites of Action: location, location, location
<table>
<thead>
<tr>
<th>Agent (s)</th>
<th>Target (s)</th>
<th>N</th>
<th>Tumour</th>
<th>ORR</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab + octreotide</td>
<td>VEGF</td>
<td>22</td>
<td>Carcinoid</td>
<td>18%</td>
<td>16.5 mo (PFS)</td>
<td>-</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR, PDGFR, RET, FLT3</td>
<td>41</td>
<td>Carcinoid</td>
<td>2%</td>
<td>10.5 mo (TTP)</td>
<td>-</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR, PDGFR, RET, FLT3</td>
<td>66</td>
<td>PNETs</td>
<td>17%</td>
<td>7.7 mo (TTP)</td>
<td>-</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>VEGFR, PDGFR, Raf</td>
<td>51</td>
<td>Carcinoid</td>
<td>7%</td>
<td>7.8 mo (PFS)</td>
<td>-</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>VEGFR, PDGFR, Raf</td>
<td>42</td>
<td>PNETs</td>
<td>17%</td>
<td>11.9 mo (PFS)</td>
<td>-</td>
</tr>
<tr>
<td>Vatalanib</td>
<td>VEGFR, PDGFR</td>
<td>11</td>
<td>GEPNET</td>
<td>0%</td>
<td>NR</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEGFR, PDGFR,</td>
<td>30</td>
<td>Carcinoid</td>
<td>-</td>
<td>-</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEGFR, PDGFR,</td>
<td>30</td>
<td>PNET</td>
<td>-</td>
<td>-</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Motesanib</td>
<td>VEGFR, PDGFR, RET</td>
<td>44</td>
<td>LGNET</td>
<td>-</td>
<td>-</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Atiprimod</td>
<td>Unclear</td>
<td>25</td>
<td>LGNET</td>
<td>0%</td>
<td>76% at 6 mo (TTP)</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Bevacizumab + 2-methoxyestradiol</td>
<td>VEGF</td>
<td>31</td>
<td>Carcinoid</td>
<td>0</td>
<td>Median PFS not reached at 8.9 mo</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

Adapted from Phan and Yao
mTOR Pathway is Deregulated by Mutations in Cancer

Normal cell growth, proliferation, and metabolism are maintained by a number of mTOR regulators. Regulators of mTOR activity include mTOR activating and mTOR deactivating factors. Deregulation of mTOR can result in loss of growth control and metabolism (TSC1/2, IGF/-R, VHL). Mutations in the mTOR pathway have been linked to specific cancers.

Octreotide LAR

- Normal cell growth, proliferation, and metabolism are maintained by a number of mTOR regulators.
- Regulators of mTOR activity:
  - mTOR activating
  - mTOR deactivating
- Deregulation of mTOR can result in loss of growth control and metabolism (TSC1/2, IGF/-R, VHL)
- Mutations in the mTOR pathway have been linked to specific cancers.
Somatostatin receptor mediated effects on cell function

Somatostatin receptors are G-protein-coupled receptors that mediate the inhibition of a large number of endocrine secretory processes.

Based on their structure and function, somatostatin receptors can be divided into five subtypes, $\text{sst}_{1-5}$. 
RADIANT 3: Everolimus vs. Placebo in PNET
RADIANT 3: Everolimus vs. Placebo in PNET

![Graph showing best percentage change from baseline in size of target lesions for Everolimus (N=191) and Placebo (N=189).]

<table>
<thead>
<tr>
<th>Change in Size of Target Lesions</th>
<th>Everolimus</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in size of target lesions from baseline</td>
<td>123 (64.4%)</td>
<td>39 (20.6%)</td>
</tr>
<tr>
<td>No change in size of target lesions from baseline</td>
<td>11 (5.8%)</td>
<td>10 (5.3%)</td>
</tr>
<tr>
<td>Increase in size of target lesions from baseline</td>
<td>43 (22.5%)</td>
<td>112 (59.3%)</td>
</tr>
</tbody>
</table>
Potential Mechanisms of Escape from Response
Impact of Sunitinib on the Longest Diameters of Target Lesions

In patients with progressive, well-differentiated pancreatic NET, sunitinib 37.5 mg/day CDD resulted (vs. placebo) in:

- Significant improvement in PFS: 11.4 vs. 5.5 mo, HR 0.42, P<0.001
- Improvement in overall survival: HR 0.41, P=0.02
- Clinically significant increase in response rate: 9.3% vs 0%, P=0.007

Improvements in PFS was seen in all subgroups

Adverse events with sunitinib were tolerable and manageable by dosing interruption/reduction and/or standard medical therapy

- The most frequent events were consistent with previous trials of sunitinib
- Rates of asthenia, vomiting and fatigue were similar in both arms

These data support the clinical safety and efficacy of sunitinib in patients with advanced pancreatic NET

Combination Therapies?
Rationale for mTOR Combinations

- Normal cell growth, proliferation, and metabolism are maintained by a number of mTOR regulators.
- Regulators of mTOR activity:
  - mTOR activating
  - mTOR deactivating
- Deregulation of mTOR can result in loss of growth control and metabolism (TSC1/2, IGF/-R, VHL)
- Mutations in the mTOR pathway have been linked to specific cancers

Octreotide LAR

- Normal cell growth, proliferation, and metabolism are maintained by a number of mTOR regulators.

Cell Growth & Proliferation

Bioenergetics

Angiogenesis

Cancer Cell

PTEN

TSC1

TSC2

mTOR

PI3K

Akt

Abl

ER

Ras

EGF

IGF

VEGF

Growth Signaling

Nutrients

Protein Synthesis

Everolimus

Octreotide LAR
RADIANT 2: Everolimus/LAR vs LAR in iNET

Graph A:
- Proportion event free (%)
- Number at risk
  - E+O: 216, 202, 167, 129, 122, 102, 81, 76, 63, 58, 50, 42, 33, 32, 22, 22, 17, 11, 11, 4, 1, 1, 0
  - P+O: 213, 201, 155, 117, 106, 84, 72, 55, 57, 50, 42, 35, 24, 18, 11, 9, 3, 1, 0, 0
  - HR: 0.77 (95% CI: 0.59-1.00)
  - p = 0.026

Graph B:
- Proportion event free (%)
- Number at risk
  - E+O: 216, 199, 167, 129, 119, 100, 81, 74, 68, 62, 51, 40, 32, 24, 18, 11, 11, 4, 2, 1, 0
  - P+O: 213, 201, 159, 121, 114, 92, 75, 72, 64, 56, 50, 41, 27, 21, 11, 10, 4, 1, 0, 0
  - HR: 0.78 (95% CI: 0.52-0.98)
  - p = 0.018
Temozolomide (Temodar)
Oral chemotherapy
Used for Grade IV astrocytoma — tumor
Converted to imidazotetrazine-derivative of dacarbazine
Damages DNA
Tumors fight back with: O-6-methylguanine-DNA methyltransferase (MGMT)
Tumors with low MGMT: may be more vulnerable to this drug
Capectabine (xeloda)-5FU
### Efficacy of Temozolomide in NETs

**Table 4. Efficacy**

<table>
<thead>
<tr>
<th>Response</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td><strong>Radiologic</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1</td>
</tr>
<tr>
<td>Partial response</td>
<td>6</td>
</tr>
<tr>
<td>Carcinoid (n = 14)</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic neuroendocrine tumor (n = 11)</td>
<td>5</td>
</tr>
<tr>
<td>Pheochromocytoma (n = 3)</td>
<td>1</td>
</tr>
<tr>
<td>Complete + partial response</td>
<td>7</td>
</tr>
<tr>
<td>Stable disease</td>
<td>19</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
</tr>
<tr>
<td><strong>Biochemical (chromogranin A; n = 20 assessable)</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>8</td>
</tr>
<tr>
<td>Stable disease</td>
<td>7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5</td>
</tr>
</tbody>
</table>

J Clin Onc; 2006
...but tolerability???

<table>
<thead>
<tr>
<th>Reason off Study</th>
<th>Patients</th>
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<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Treatment-related toxicity*</td>
<td>16</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4</td>
</tr>
<tr>
<td>Patient withdrew consent</td>
<td>4</td>
</tr>
<tr>
<td>Patient was noncompliant</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
</tbody>
</table>

*Treatment-related toxicities resulting in discontinuation: neuropathy (six patients), infection (four patients), thrombocytopenia (four patients), neutropenia (one patient), rash (one patient). Infections included: Pneumocystis carinii pneumonia (one patient), disseminated varicella zoster virus (one patient), staphylococcal sepsis (one patient), cutaneous herpes zoster (one patient).
Bevacizumab + Octreotide in NET

1471-2407-14-184. Bevacizumab plus octreotide and metronomic capecitabine in patients with metastatic well-to-moderately differentiated neuroendocrine tumors: the xelbevoc study
Management Approaches

Metastatic NET

Surgery (resection, debulking RF, embolization), Repeat Surgery

WHO 1
Ki-67 <2%

WHO 2
Ki-67 >2-20%

WHO 3
Ki-67 >20%

Biotherapy
- Somatostatin analogue (SMS)
- α-IFN
- Bevacizumab

Chemotherapy
- STZ+5FU/Dox
- STZ + Everolimus
- Temozolomide
- Temozolomide + capecitabine (CAPTEM)

Chemotherapy:
Cispl + Etoposide
Temozolomide

Combinations
- SMS + α-IFN
- SMS + everolimus
- SMS + bevacizumab
- SMS + sunitinib

Targeted Radiotherapy
Lu^{177} DOTA-TATE

SMS for symptom control
+ capecitabine
+ bevacizumab
SMS for symptom control
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