Diagnosis and Treatment of Neuroendocrine Tumors

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SON Fall Update
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Objectives

• Review incidence and survival of NETs.

• Present new terminology and classification.

• Consider NET treatment options
Incidence of neuroendocrine tumors (NETs) over time, by site and by disease stage

Diagnosis

• Pathological:
  – IHC: Synaptophysin, Chromogranin

• Active versus Inactive:
  – 30-50% hypersecretion syndromes
  – Foregut: peptides (insulin, glucagon, VIP, gastrin)
  – Midgut: biogenic amines (serotonin, tachykinins)
  – Not prognostic, but influence management
Confusing Terminology

Carcinoid

Atypical carcinoids

Insulinoma

Islet cell tumor

Neuroendocrine Carcinoma

Large Cell Neuroendocrine Carcinoma

ENTES Classification and Staging

WHO Classification

AJCC Staging
Convergence of Classification

• Use NET: Neuroendocrine Tumors
  – Foregut: Lung, Gastric, Pancreas
  – Midgut: Small bowel, Appendix
  – Hindgut: Large Bowel, Rectum

• Exclude NEC: Neuroendocrine CARCINOMAS.
## NET vs NEC

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic Count</th>
<th>Ki-67</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 fields at 40x</td>
<td>% of 2000 tumor cells</td>
</tr>
<tr>
<td>G1</td>
<td>&lt;2</td>
<td>≤2</td>
</tr>
<tr>
<td>G2</td>
<td>2-20</td>
<td>3-20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
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</table>
Therapeutic Options
LOCAL and REGIONAL Disease

– RESECTION

– Adjuvant therapy is not currently indicated in completely resected NETs
Advanced NETs: Therapeutic Options

- RESECTION and ABLATION

- Radioparticle therapy

- Octreotide and Interferon therapy

- Chemotherapy

- Small molecule targeted therapy
Resectable metastatic disease is treated with curative surgical intent.

Unresectable bulky or symptomatic tumors are treated with surgical DEBULKING.

Numerous case series report 5 year survival of 50-70% among resected patients.
Non-Resectable Hepatic Disease

- If NOT resectable:
  - Ablate, Embolize, Radiate.

- No randomized trials evaluating these techniques
CAUTION: Carcinoid crisis and hepatic directed therapy!!!
Radiation Source: Yttrium-90

- 99.97% $\beta$ radiation (‘pure’)
- Penetration range = 11mm
- Half-life = 64.2 hours and decays to stable zirconium-90
- Intra-arterial administration – Not truly embolic.
- Response rates variable

Courtesy D Liu
Peptide Receptor Radiotherapy

- Radioactive isotopes attached to octreotide: Lutetium, Indium, Yttrium

- LU-Octreotate among the best evidence:
  - Response Rate 30% in Single Institution
  - Now Available in CANADA!

- Octreoscan positivity (ie. positive Indium$^{111}$ scintigraphy) is a requirement for therapy.

Kwekkeboom JCO 2008
Therapeutic Options

- Resection and Ablation
- Radioparticle therapy
- OCTREOTIDE AND INTERFERON
- Chemotherapy
- Small molecule targeted therapy
Human somatostatin

Octreotide acetate

Ilanreotide
Somatostatin Analogs: SSA

• Somatostatin analogs bind to somatostatin receptors
• Current indication is for control of symptoms related to FUNCTIONAL neuroendocrine tumors.
• Biochemical responses > 70% and objective response < 5%
• What about use to control disease?
Primary endpoint: time to tumor progression

- Treatment was continued until CT or MRI documented tumor progression.
Patient population

• Newly diagnosed and treatment naïve

• Histologically confirmed, locally inoperable or metastatic well-differentiated midgut NETs.

• ACTIVE or INACTIVE
Octreotide LAR significantly increases time to tumor progression

Octreotide LAR vs placebo $P=0.000072$

$HR=0.34$ [95% CI: 0.20–0.59]

Octreotide LAR: 42 patients / 26 events
Median 14.3 months [95% CI: 11.0–28.8]

Placebo: 43 patients / 40 events
Median 6.0 months [95% CI: 3.7–9.4]

Based on the conservative ITT analysis
Overall survival

Octreotide LAR median survival duration not yet reached (>77.4 months)
Placebo: 73.7 months

Octreotide LAR: 42 patients / 7 events
Median >77.4 months (not reached)

Placebo: 43 patients / 9 events
Median 73.7 months
Therapeutic Options

- Resection and Ablation
- Radioparticle therapy
- Octreotide
- CHEMOTHERAPY
- Small molecule targeted therapy
Chemotherapy

- PNETs are generally more chemosensitive than other NETs.

- Benefit hard to quantify as chemotherapy trials included non-PNETs and no phase III randomized trials.

- Alkylating agents are active in pancreatic NETs.
Therapeutic Options

– Resection and Ablation
– Radioparticle therapy
– Octreotride and IFN
– Chemotherapy
– SMALL MOLECULE TARGETED THERAPY
Targeted Therapy for NETs

- Sutent – Tyrosine Kinase inhibitor
- Everolimus – mTOR inhibitor
- Sutent and Everolimus developed in PNETs

- Phase III trial of Everolimus in NET did not demonstrate superiority over placebo
Everolimus for Advanced Pancreatic Neuroendocrine Tumors

James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D., Catherine Lombard Bohas, M.D., Edward M. Wolin, M.D., Eric Van Cutsem, M.D., Ph.D., Timothy J. Hobday, M.D., Takuji Okusaka, M.D., Jaume Capdevila, M.D., Elisabeth G.E. de Vries, M.D., Ph.D., Paola Tomassetti, M.D., Marianne E. Pavel, M.D., Sakina Hoosen, M.D., Tomas Haas, Ph.D., Jeremie Lincy, M.Sc., David Lebwohl, M.D., and Kjell Öberg, M.D., Ph.D., for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group

ABSTRACT
RADIANT-3: Study Design

Patients with advanced pNET  
$n=410$

Randomize

1:1

Cross over

Everolimus 10 mg/d + best supportive care*

Placebo + best supportive care*

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

Randomization  Aug. 2007 – May. 2009

*concurrent somatostatin analogs allowed
Primary Endpoint: PFS by Treatment

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
Phase III, Randomized, Double-Blind Study of Sunitinib vs. Placebo in Patients with Progressive, Well-Differentiated Pancreatic NET

Eligibility criteria
- Well-differentiated, malignant pancreatic endocrine tumor
- Disease progression in past 12 months
- Not amenable to treatment with curative intent

Balanced by region
- Europe, Asia, Americas/Australia

N=340 planned
N=171 randomized

Sunitinib 37.5 mg/day orally, continuous daily dosing (CDD)*

Primary endpoint: PFS

Secondary endpoints:
- OS, ORR, TTR, duration of response, safety, patient-reported outcomes

Placebo*

After trial closure (due to differences in deaths, serious AEs and PFS), patients became candidates for open-label sunitinib in trial NCT00443534 or NCT00428220

*With best supportive care. Somatostatin analogs were permitted
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
- Sunitinib: 86, 39, 19, 4, 0, 0
- Placebo: 85, 28, 7, 2, 1, 0
CONCLUSIONS

- NETs represent heterogeneous but distinct clinical group.
- Consider as biologically distinct tumors, regardless of site of origin
- Surgical resection is paramount
- For non-resectable disease, increasing number of hepatic directed options.
CONCLUSIONS

• Octreotide primarily for FUNCTIONAL tumors.

• Consider PNETS for systemic therapy (chemo, everolimus, sutent).

• Consider ablative therapies and clinical trials for NETs.