Neuroendocrine Tumors: benefit of therapies, beyond chemotherapy

I Congresso de Oncologia D’Or 2013

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Disclosures

• No relevant financial disclosures
Objectives

• Review basic biology of neuroendocrine tumors
  – Classify
  – Differentiate

• Review historical therapeutic paradigms

• Review locoregional therapy options
  – Liver-directed therapy

• Review recent approvals of targeted therapies
  – Everolimus
  – Sunitinib
Neuroendocrine tumors

• Wide spectrum of malignancies
• Arise in neuroendocrine cells throughout the body
• Characterized by production of biogenic amines and polypeptide hormones – specific products determined by the cell location and role in normal physiology
• Can have benign or malignant behaviors
• Traditionally difficult to classify due to variant behavior
Neuroendocrine tumors

• Epidemiology:
  – 80% of all NET are either carcinoid or pancreatic NET
  – Male predominance, average age of diagnosis: 60
  – Carcinoid tumor
    • Prevalence estimates up to 1.2% of general population
    • Incidence difficult to quantify as majority go undetected
    • Common sites include small bowel, lung, other GI tract site
  – Pancreatic neuroendocrine tumor
    • Clinical incidence: 1 in 100,000
    • Autopsy prevalence: 300 in 100,000
    • Can be non-functional or hormone-producing (insulinoma etc.)
<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Grade</th>
<th>Mitotic count*</th>
<th>Ki-67 index*</th>
<th>Traditional</th>
<th>ENETS, WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>Low grade (G1)</td>
<td>&lt;2 per 10 HPF</td>
<td>&lt;3 percent</td>
<td>Carcinoid, islet cell, pancreatic (neuro)endocrine tumor</td>
<td>Neuroendocrine tumor, Grade 1</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td></td>
<td></td>
<td>Carcinoid, atypical carcinoid⁵, islet cell, pancreatic (neuro)endocrine tumor</td>
<td>Neuroendocrine tumor, Grade 2</td>
</tr>
<tr>
<td></td>
<td>grade (G2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>High grade (G3)</td>
<td>&gt;20 per 10 HPF</td>
<td>&gt;20 percent</td>
<td>Small cell carcinoma</td>
<td>Neuroendocrine carcinoma, Grade 3, small cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Large cell neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma, Grade 3, large cell</td>
</tr>
</tbody>
</table>

ENETS: European Neuroendocrine Tumor Society; WHO: World Health Organization.

* Counted in 10 high power fields (HPF). 10 HPF = 2 mm², at least 40 fields (at 400x magnification) evaluated in areas of highest mitotic density. Cut-offs per American Joint Commission on Cancer Staging Manual, 7th edition.


Δ The term "atypical carcinoid" only applies to intermediate grade NETs of the lung.

WHO classification 2010

Has largely replaced the older, anatomic site-based classifications
Well-differentiated and poorly-differentiated NET are on the same spectrum of disease, but have markedly different behaviors, prognosis and treatment response.

Accurate pathologic interpretation is key to steering patients on the appropriate treatment path.
Differentiating NET

• WHO Classification
  – Valid for tumors arising in the gastroenterohepatic systems
  – Does not hold up as well for NET of unknown primary site

  – Provides accurate prognostic ability based upon tumor grade
    • 5yr survival for Grade 1, 2 and 3 tumors is 75%, 62% and 5% respectively
    • Many patients with Grade 1 disease can live for decades (truly benign histology)
Therapeutic options

• Treatment is indicated for a variety of reasons:
  – Expected disease biology based on grade etc.
  – Symptoms of hormone hypersecretion
  – Symptoms of tumor bulk

  – The majority of gastroenterohepatic NET will exhibit liver metastases, so liver-directed therapy has been a mainstay of interventional treatments for some time
  – Appropriate timing of interventions is a key point to consider
Surgical intervention

• Formal surgical resection of NET liver metastases was commonly performed, as there was evidence for long term disease control
• However, recent series suggest that almost 100% of patients will exhibit recurrent disease post ‘curative’ resection
  – Many groups are now avoiding major hepatectomy in these patients
  – There can be rationale for resection of primary site (especially in the small bowel) to minimize local symptoms in that region
Surgical debulking

• Also once popular, with a goal of removing up to 90% of visible tumor burden
• The goal of such interventions was to minimize symptomatology and maximize DFS
  – A number of retrospective series suggested benefit in the regard, but with the advent of less invasive liver-directed modalities, it has also fallen out of favor.
  – It is now rare for patients to undergo major surgical interventions for these indications.
Embolotherapies

- Indicated for reduction of symptoms (bulk, hormones) in patients with liver dominant disease

- TAE/TACE
  - No level 1 evidence
  - Case series: 81 pts, advanced carcinoid, liver mets; median response duration 17 mo; PFS at 1,2,3 yrs, 75%, 35%, 11%

- Y90 Radioembolization
  - Similarly limited experience
  - 148 pt series, 64% RR, limited duration, but good symptom control
Systemic therapies

• Symptom management
  – Somatostatin analogs:
    • Effective at controlling symptoms of hormone excess, especially in patients with carcinoid, and functional pancreatic NET.
    • Short-acting Octreotide used to ameliorate symptoms, before transitioning to treatment with longer-acting forms such as Octreotide LAR, or Lanreotide
    • Toxicities include: impaired glucose metabolism, malabsorptive symptoms, asymptomatic gall stones.
    • Will generally control symptoms in the long term
    • IFN can be useful if symptoms recur while on these analogs.
Systemic therapies

• Anti-cancer therapies
  – Somatostatin analogs
    • Good evidence of control in carcinoid tumors
  – Cytotoxic chemotherapy
    • Reasonable response rates in pancreatic NET, but toxic
  – Molecularly targeted therapy
    • Evidence of efficacy across tumor types, but better in pancreatic NET than carcinoid
  – Systemic radionuclide therapy
    • Targeting radioisotopes using somatostatin tags
Cytotoxic chemotherapy

• Definitively indicated in poorly differentiated NET, which behave like small cell lung carcinoma
  – Platinum, etoposide combination.
  – Robust response, but often not durable

• Historically utilized in intermediate grade NET and carcinoid, with some series indicating encouraging response rates, but significant toxicity
  – Streptozocin
  – Doxorubicin
  – Dacarbazine/temozolomide
  – Platinum agents
Molecularly targeted therapy

• Rationale
  – NET exhibit upregulation/overexpression of a series of growth factors/receptors (VEGF, PDGF, IGF), as well as enhanced signaling through intracellular pathways, notably mTOR.
  – Preclinical models indicated impaired NET cell growth with inhibition of these targets.
  – Clinical studies undertaken, focusing on mTOR inhibition and angiogenesis inhibitors.
Molecular targets in NET

- Endothelial cells
- Pericytes
- Neuroendocrine cells

**VEGFR**
- Sunitinib
  - PI3k
  - AKT
  - mTOR

**PDGFR**
- Somatostatin
  - SSR
  - Somatostatin analogues

Inhibition of tumour angiogenesis

Source: Ther Adv Med Oncol © 2011 SAGE Publications Ltd
Everolimus in pancreatic NET

- RADIANT-3 trial.
  - 410 patients, radiographically progressive NET, low-intermediate grade; randomized to Everolimus 10mg daily vs. placebo.
  - Median PFS 11mo vs. 4.6mo, favoring Everolimus (HR 0.35)
  - Crossover allowed so no OS endpoint reported

- Risks: stomatitis, rash, fatigue, diarrhea, elevated cholesterol, elevated glucose

PFS, Everolimus vs. placebo

Hazard Ratio = 0.35
95% CI [0.27, 0.45]
Logrank p value = <0.001

Kaplan-Meier medians
Afinitor: 11.04 months
Placebo: 4.60 months

Probability (%) vs. Time (months)
Sunitinib in pancreatic NET

- Phase 3 trial:
  - 171 patients, radiographically progressive panc NET, randomized to Sunitinib 37.5mg daily vs. placebo.
  - Median PFS 11.5mo vs. 5.5mo, favoring Sunitinib
  - Trial stopped at first interim analysis due to this favorable result
  - No OS data presented due to truncation of study.

  - Toxicities included asthenia, fatigue, diarrhea, nausea, vomiting.

PFS, Sunitinib vs. placebo

SUTENT (N=86)
Median 10.2 months

Placebo (N=85)
Median 5.4 months

Hazard Ratio = 0.427
95% CI (0.271 - 0.673)
p = 0.000146

Number of subjects at risk
SUTENT  86   53   35   19   14   4   1
Placebo 85   41   16   8    2    2   2
Octreotide in carcinoid tumor

- PROMID study.
  - 85 treatment naïve patients with midgut carcinoid, low proliferative index (<2%), asymptomatic.
  - Randomized to Octreotide (30mg monthly) vs. placebo
  - Median TTP 14.3mo vs. 6mo, favoring Octreotide, with 2/3 patients remaining without progression at 6 months.
  - Crossover allowed and trial stopped at interim analysis so no OS data assessed.
PROMID PFS curves

Figure 1 - Kaplan-Meier plot of time to progression or tumor-related death. ITT analysis.
Systemic radionuclide therapy

- Radiolabeled somatostatin analogs, typically Y90 or Lu177.
- Widely deployed in Europe, still under investigation in the US.
  - Y90 study: 1109 pts, metastatic NET, positive Octreoscan. 34% morphologic response, 15% biochemical response, 30% symptomatic improvement. Median OS 94mo, major limiting toxicity is renal damage
  - Lu177: RR around 30% in select patients.
Treatment summary

• Carcinoid
  – Somatostatin analog for patients with symptoms or disease progression
  – Liver-directed therapy for bulky/progressive liver mets
  – No impact with cytotoxic chemotherapy
  – Some impact with Everolimus, but clinical trial preferred

• Panc NET
  – Liver-directed therapy for bulky/progressive disease
  – First line therapy with Everolimus or Sunitinib for disease progression
  – Some impact with cytotoxic chemotherapy (Temozolomide)
  – Somatostatin analogs for hormonal symptoms
  – Consider radionuclide therapy if available, or clinical trial
Take home message

• Do all cases of neuroendocrine tumor mandate therapy?
  • No!
  – Low grade NET will have an indolent biology in many cases
  – All systemic therapy trials enrolled patients with radiographic disease progression within 6 months, so it is unclear what impact, if any, these agents will have in a slower growing tumor
  – Apart from tumor grade, there are some other biomarkers of disease biology we can focus on
Whole genome sequencing, NET set

<table>
<thead>
<tr>
<th>Genes</th>
<th>Frequency Mutated (n=68)</th>
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<tbody>
<tr>
<td>MEN1</td>
<td>44% (30)</td>
</tr>
<tr>
<td>DAXX</td>
<td>25% (17)</td>
</tr>
<tr>
<td>ATRX</td>
<td>18% (12)</td>
</tr>
<tr>
<td>PTEN</td>
<td>7% (2)</td>
</tr>
<tr>
<td>TSC2</td>
<td>9% (6)</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>1% (1)</td>
</tr>
</tbody>
</table>

• Mutually Exclusive
• Proteins form a Complex
Summary

• NET therapy more advanced in recent years
• Initial discussion is ‘to treat or not to treat’ – guided by accurate pathology and molecular markers
• Panc NET is more responsive to systemic therapy than carcinoid
• Molecularly targeted agents all approved via improved PFS, no OS data provided
• Further delineation of these tumors will come on stream in the years ahead