Teamwork Makes the Dream Work:
Working with medical oncologists to deploy PRRT strategically

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Disclosures

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- Research funded by Ipsen, Genentech, Novartis, Tarveda, ThermoFisher Scientific.
- I will discuss off-label and/or investigational use [temozolomide].
Objectives

1. Share a single common framework for classifying NENs
2. Understand systemic therapy options for NET patients
3. Propose a systematic approach to treatment recommendations
## Framework

<table>
<thead>
<tr>
<th>Grade 1-2 NET Pancreatic Primary</th>
<th>Grade 1-2 NET Extrapancreatic Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 NET Pancreatic Primary</td>
<td>Grade 3 NET Extrapancreatic Primary</td>
</tr>
<tr>
<td></td>
<td>Grade 3 NEC Any Primary</td>
</tr>
</tbody>
</table>
Grading NENs (2017)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; 2 mitoses/10 HPF, Ki-67 &lt;3%</td>
</tr>
<tr>
<td>2</td>
<td>2-20 mitoses/10 HPF, Ki-67 3-20%</td>
</tr>
<tr>
<td>3 NET</td>
<td>Well-differentiated</td>
</tr>
<tr>
<td></td>
<td>&gt;20 mitoses/10 HPF, Ki-67 &gt;20%</td>
</tr>
<tr>
<td>3 NEC</td>
<td>Poorly-differentiated</td>
</tr>
<tr>
<td></td>
<td>&gt;20 mitoses/10 HPF, Ki-67 &gt;20%</td>
</tr>
</tbody>
</table>

Grade is dependent on appearance and rate of cellular division
Grade, Stage, Primary Site

<table>
<thead>
<tr>
<th>Primary Tumor Site</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix</td>
<td>NA</td>
</tr>
<tr>
<td>Cecum</td>
<td>98</td>
</tr>
<tr>
<td>Colon</td>
<td>14</td>
</tr>
<tr>
<td>Lung</td>
<td>24</td>
</tr>
<tr>
<td>Pancreas</td>
<td>60</td>
</tr>
<tr>
<td>Rectum</td>
<td>33</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>103</td>
</tr>
<tr>
<td>Stomach</td>
<td>29</td>
</tr>
</tbody>
</table>

Yao et al., J Clin Oncol 2008; 26:3063

Dasari et al., JAMA Oncol. 2017 Oct 1;3(10):1335-1342
Management Options
Management Principles

• Removal of localized and limited metastatic disease

• Advanced disease
  • Control of hormone secretion
  • Control of tumor growth
  • Minimize toxicity

Surgical to Medical: Nuclear Medicine -> Interventional
Streptozocin in pNET

- Streptozocin: “islet-specific” alkylator.
- Initially tested in 4 pNET and 4 carcinoid patients at NCI.
- 1 CR for 1 year in pNET patient.
- 3 subsequent prospective randomized studies confirmed efficacy.
- However, radiographic response rates with doublets were < 10%.
- The triplet of FAS has been reported to yield a response rate of 40%.
- Characteristic toxicities include neutropenia, hair loss, nausea/vomiting, possible cardiac toxicity.

Moertel et al., N Engl J Med 1980; 303:1189

<table>
<thead>
<tr>
<th>Category</th>
<th>Streptozocin Alone</th>
<th>Streptozocin Plus Fluorouracil</th>
<th>Median Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All responses</td>
<td>15/42 (36)</td>
<td>25/40 (63)</td>
<td>17</td>
</tr>
<tr>
<td>Complete responses</td>
<td>5/42 (12)</td>
<td>13/40 (33)</td>
<td>24</td>
</tr>
</tbody>
</table>

*Data are reported as in Table 3. Figures in parentheses denote percentages.
†P<0.01.
‡P>0.01.

Capecitabine/Temozolomide (CAPTEM) in pNET

<table>
<thead>
<tr>
<th>AE Category</th>
<th>AE Term</th>
<th>TEM (n=68)</th>
<th>CAPTEM (n=72)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst degree for all treatment-related, Grade 3-4 AEs</td>
<td>22%</td>
<td>44%</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Treatment-related, Grade 3-4 AEs &gt; 5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Neutropenia</td>
<td>4%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td>4%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>13%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>0%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>0%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>0%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Constitutional</td>
<td>Fatigue</td>
<td>1%</td>
<td>8%</td>
<td></td>
</tr>
</tbody>
</table>

Confirmed ORR 33.3% vs. 27.8% (p=0.47)

Kunz et al., ASCO 2018
Sunitinib in pNET

- Sunitinib: PO VEGFR inhibitor
- Patients with G1-2 advanced pNETs, PD within 12 months.
- Sunitinib vs. placebo.

Somatostatin analogues in GEP-NET

Rinke et al., J Clin Oncol 2009; 27:4656
Everolimus in pNET and non-functional epNET

<table>
<thead>
<tr>
<th>Grade</th>
<th>pNET</th>
<th>epNET</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Yao et al., *Lancet* 2016; 387: 968–77

Figure 2: Progression-free and overall survival (full analysis set)
Kaplan-Meier curves of (A) progression-free survival as assayed by central radiology review, (B) progression-free survival as assessed by local investigators, and (C) overall survival. HR= hazard ratio. "The Lan-DeMets O'Brien-Ponzaing boundary for significance at first interim analysis was 0.9992."
PRRT in midgut NET

- NETTER-1

- $^{177}$Lu-DOTA-Octreotate (DOTATATE): a radioactive isotope conjugated to somatostatin analogue.

- Patients with G1-2 midgut NET, PD on octreotide LAR 30, somatostatin-avid.

- DOTATATE vs. octreotide LAR 60mg.

PFS HR 0.209 [95% CI 0.129-0.33]  
Strosberg et al., NEJM 2017; 376:125-135
Treatment Paradigm
The Therapeutic Ladder

PRRT (\textsuperscript{177}Lu-DOTATATE)

Chemotherapy\(^*\)
(Streptozocin, Temozolomide)

Targeted therapies
(Everolimus, Sunitinib\(^*\))

Somatostatin Analogues
(Octreotide/Lanreotide)

Observation

*Pancreatic NET only

Liver-directed Therapy

Tolerability

Response Rate
Inoperable Therapeutic Approach

Advanced NET

High Volume

Progressive

Cytotoxic

Liver-directed

Sunitinib

Everolimus

Low Volume

Indolent

Progressive

Cytotoxic

SSA

Observation

Indolent
Thank you!

- Questions and discussion welcome

Our Team

Nuclear Medicine
- Beth Chasen
- Leslie Flynt

Interventional Radiology
- Armeen Mahvash
- Rony Avritscher
- Joshua Kuban

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