MEDICAL MANAGEMENT OF METASTATIC GEP-NET

Jeremy Kortmansky, MD
Associate Professor of Clinical Medicine
Yale Cancer Center

DISCLOSURES: NONE
Introduction

- Gastrointestinal and pancreatic neuroendocrine tumors are often treated with similar paradigms.
- However, there is real variability in biology, prognosis and treatment response based on location.
- Majority are “non-functional” – do not secrete, or secrete inactive proteins
- Highly variable tumor behavior
  - Some are indolent for years or decades
  - Some symptomatic from tumor bulk or peptide hormone hypersecretion
Introduction

- Prognosis driven by location and histologic grade
- Rectum > small bowel > pancreas > colon
- Histologic grade – Ki-67 index
  - Neuroendocrine tumor
    - Well-differentiated, grade 1 (< 2%)
    - Well-differentiated, grade 2 (2-20%)
    - Well-differentiated, grade 3 (20-55%)
  - Neuroendocrine carcinoma
    - Poorly differentiated – treated like small cell cancer
- Sensitivity to systemic therapies
  - Pancreas >> carcinoid
Management

- Initial management may be observation
- Indication for treatment:
  - Pain
  - Symptoms from hormone secretion
  - High tumor burden
  - Progression of disease under observation
Management

• Treatment algorithm for metastatic disease
  • Potentially Resectable
  • Unresectable, Asymptomatic
  • Unresectable, Symptomatic
  • Therapy at Progression
Management

- Treatment options include:
  - cytoreductive surgery
  - liver directed therapy
  - somatostatin analogues
  - anti-angiogenic agents
  - mTOR inhibitors
  - Chemotherapy
  - PRRT
Long-acting somatostatin analog therapy

Symptoms controlled?

Yes
- Continue long-acting somatostatin analog

No
- Escalate dose of long-acting somatostatin analog

Progression

Hepatic predominant disease?

Yes
- Debulking surgery or nonsurgical liver-directed therapy

Progression

Systemic therapy

No
Systemic therapy

Tumor expresses somatostatin receptors?

No

Everolimus

Yes

Everolimus or radiolabeled somatostatin analog, where available
PNET Treatment Algorithm

uptodate 2018

Systemic therapy

Tumor expresses somatostatin receptors?

- No
  - anti-angiogenic agents
  - mTOR inhibitors
  - Chemotherapy

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  +

  - anti-angiogenic agents
  - mTOR inhibitors
  - Chemotherapy
Cytoreductive surgery

- Indolent tumors with relative low burden of disease
- Should include resection of primary pancreatic neoplasm
- Can be used in conjunction with systemic therapies, for example, somatostatin analogues
Liver directed therapy

- Yttrium-90
- Transarterial chemoembolization (TACE)
- Hepatic artery embolization or bland embolization
- Ablation
- Surgery
Somatostatin analogues

- More than 75% of GEP-NET express somatostatin receptors, most commonly SST-2, and are octreotide avid on somatostatin analogue scintigraphy.

- Synthetic analogues: Octreotide and Lanreotide

- Highly active in patients with functional tumors; e.g. – VIPoma and insulinoma, or serotonin-secreting
  - Use with caution in insulinoma for possible profound hypoglycemia
  - Gastrinomas – PPI preferred
Somatostatin analogues, cont’d

- Non-functioning tumors, progressive
  - PROMID\(^1\) study for patients with progressive carcinoid tumors
    - 85 patients randomized to octreotide LAR 30 mg or placebo
    - TTP: 14.3 mos versus 6 months (\(p < 0.000072\))
    - NCCN has extrapolated this data to panNET, as well, but, in fact, no randomized data exist
  - CLARINET\(^2\)
    - 204 patients randomized, 45% with panNETs
    - Lanreotide 120 mg versus placebo
    - PFS: not reached versus 18 mos (\(p < 0.001\))
    - No difference in QOL or OS

Antiangiogenic agents

- PNETs are highly vascular, and frequently overexpress the vascular endothelial growth factor (VEGF) ligand and receptor

- Sunitinib versus placebo (no catchy name)*
  - 37.5 mg continuous daily dosing
  - Discontinued after 171 patients following interim analysis
  - PFS 11.4 versus 5.5 months; RR: 9.3% versus 0%
  - Trend towards improvement in OS
    - 33 mos vs 26.7 months, p <0.11
  - Study allowed access to sunitinib after progression
  - Side effects: diarrhea, nausea, vomiting

mTOR inhibitors

- About 15% of patients with pancreatic NETs have somatic mutations along the mTOR pathway. Unknown for carcinoid.

- Phase II: everolimus (RAD001) + LAR
  - ORR 22%, SD 70% (carcinoid and PNET)

- RADIANT 2 trial: everolimus versus placebo
  - 429 patients with functional carcinoid tumor
  - PFS: 16.4 versus 11.3 mos (NCS)

- RADIANT 3\(^1\) trial: everolimus versus placebo
  - 410 patients with low-grade or intermediate-grade PNETs
  - PFS: 11 mos versus 4.6 mos; RR: 5% versus 2%
  - OS\(^2\): 44 mos vs 37.7 mos (p =0.30); attributed to crossover design
  - Side effects: mouth sores, rash, diarrhea, fatigue, high blood sugar and infections

Chemotherapy

- **Streptozocin**
  - 1970s, RR 63% with 5FU; 36% monotherapy
  - 1980s, ECOG study with 105 pts\(^1\)
    - RR 69% with doxorubicin; 45% with 5FU
  - Using modern assessments, RR about 40%, 2 year PFS 41%
  - All studies limited by substantial toxicity

- **Dacarbazine**
  - ECOG 6282\(^2\), phase II study of DTIC (n = 50)
  - RR 34%, OS 19 mos
  - Substantial toxicity as well.

Chemotherapy cont’d

• Temozolomide – a more pleasant DTIC

  • Temozolomide/capecitabine\(^2\): retrospective, n=30
    • RR 70%; median PFS 18 mos; 2-year OS 92%
    • Correlation with MGMT expression
    • Heme toxicity

• MGMT plays a role in metabolism of temozolomide
  • Loss of MGMT = better response to tem (we can measure in blood)
    • Loss in 65% PNET
    • Intact in carcinoid

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Chemotherapy cont’d

- ECOG 2211: Randomized phase II trial of temozolomide versus temozolomide plus capecitabine (ASCO 2018)
  - 144 patients with pancreatic neuroendocrine tumor
  - PFS 14.4 months versus 22.7 months
  - Median OS: 38 months versus not yet reached
  - RR 28% versus 33%
  - Tox: neutropenia, nausea, diarrhea, fatigue all higher with combination
On-going investigation

• Bevacizumab
  - Bevacizumab + chemotherapy
    • Temozolomide\(^1\): 15 pts with panNET: RR 33%; PFS 14.3 mos
    • FOLFOX/bevacizumab\(^2\): 6 pts: RR 33%
    • CapOx/bevacizumab\(^3\): 20 pts: RR 30%
  
• Temsirolimus/bevacizumab\(^4\)
  - 56 pts: RR 41%; PFS 13.2 mos; OS 34 mos

• CALGB 80701\(^5\): octreotide LAR + everolimus + bevacizumab or placebo
  - 150 pts: RR 31% v 12%; PFS 16.7 mos vs 14 mos (HR = 0.80)

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On-going investigation

- Cabozantinib
  - Approved for RCC and thyroid cancer
  - Targets VEGF and MET
  - MET overexpression is a poor prognostic factor
- Phase II trial*, enrolled 61 pts (PNET = 20)
  - Median 3 prior therapies
  - Primary endpoint: ORR 15%, for PNET, DCR = 75%
  - PFS: 21.8 mos
- Phase III trial randomized trial coming soon (ALLIANCE): cabozantinib versus placebo after progression on everolimus

Peptide receptor radiation therapy (PRRT) – The future is now

- **Lu-177-DOTATATE**
  - NETTER-1 ¹
  - 229 patients with well-differentiated, metastatic midgut neuroendocrine tumors
  - Randomized study:
    - Arm 1: $^{177}$Lu-Dotatate 7.4 GBq every 8 weeks for 4 treatments + octreotide LAR 30 mg every 4 weeks
    - Arm 2: Octeotide LAR 60 mg every 4 weeks
  - PFS: has not yet been reached versus 8.5 mos in high-dose octreotide LAR
  - RR 18% versus 3%

Table 4. Adverse Events (Safety Population)\(^{9}\)

<table>
<thead>
<tr>
<th>Event</th>
<th>177Lu-Dotatate Group (N = 111)</th>
<th>Control Group (N = 110)</th>
<th>p Value(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
<td>Any Grade</td>
</tr>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
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<tr>
<td>Any adverse event</td>
<td>105 (95)</td>
<td>46 (41)</td>
<td>92 (84)</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>65 (59)</td>
<td>4 (4)</td>
<td>13 (12)</td>
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<tr>
<td>Vomiting</td>
<td>52 (47)</td>
<td>8 (7)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>29 (26)</td>
<td>3 (3)</td>
<td>29 (26)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32 (29)</td>
<td>3 (3)</td>
<td>21 (19)</td>
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<tr>
<td>Distension</td>
<td>14 (13)</td>
<td>0</td>
<td>15 (14)</td>
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<tr>
<td>General disorders</td>
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<tr>
<td>Fatigue or asthenia</td>
<td>44 (40)</td>
<td>2 (2)</td>
<td>28 (25)</td>
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<tr>
<td>Edema peripheral</td>
<td>16 (14)</td>
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<td>8 (7)</td>
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<tr>
<td>Blood disorders</td>
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<td>Thrombocytopenia</td>
<td>28 (25)</td>
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<tr>
<td>Anemia</td>
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<td>6 (5)</td>
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<tr>
<td>Lymphopenia</td>
<td>20 (18)</td>
<td>10 (9)</td>
<td>2 (2)</td>
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<tr>
<td>Leukopenia</td>
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<tr>
<td>Neutropenia</td>
<td>6 (5)</td>
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<tr>
<td>Musculoskeletal disorders</td>
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<tr>
<td>Musculoskeletal pain</td>
<td>32 (29)</td>
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<td>22 (20)</td>
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<tr>
<td>Nutrition disorders</td>
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<tr>
<td>Decreased appetite</td>
<td>20 (18)</td>
<td>0</td>
<td>9 (8)</td>
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<tr>
<td>Nervous system disorders</td>
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<tr>
<td>Headache</td>
<td>18 (16)</td>
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<td>5 (5)</td>
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<tr>
<td>Dizziness</td>
<td>12 (11)</td>
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<td>Vascular disorders</td>
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<tr>
<td>Flushing</td>
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<td>1 (1)</td>
<td>10 (9)</td>
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<td>Skin disorders</td>
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<tr>
<td>Alopecia</td>
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<td>2 (2)</td>
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<td>Respiratory disorders</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>12 (11)</td>
<td>0</td>
<td>6 (5)</td>
</tr>
</tbody>
</table>
PRRT

FDA approved for somatostatin-receptor positive GEP-NETs on Jan 26, 2018 (foregut, midgut and hindgut)

Available at Yale
Immunotherapy

• Expression of PD-L1 in both tumor and infiltrating immune cells is associated with high-grade WHO classification (grade 3)\(^1\)

• The status of PD-L1 expression may be associated with progression-free survival (PFS) and overall survival

• Very few clinical trials

\(^1\)Calvacanti E, et al. Cell Death Dis 2017 Aug;8(8):e3004
Conclusion

- Better prognosis, but fewer treatment options for carcinoid tumor
- May recognized therapies for metastatic pancreatic endocrine neoplasms
  - Local therapy: surgery, IR
  - Somatostatin analogues
  - Sunitinib
  - Everolimus
  - Chemotherapy: temozolomide, platinum-based regimens
  - PRRT
- There are no head to head comparisons so all are appropriate; the challenge is in the sequencing.
Thank you for your attention