MEDICAL MANAGEMENT OF METASTATIC PANCREATIC ENDOCRINE NEOPLASMS

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DISCLOSURES: NONE
Introduction

- 3% of pancreatic tumors, but incidence increasing
- Develop from endocrine tissue of pancreas (islets of Langerhans)
- 1/3 are functional tumors secrete insulin, gastrin, glucagon, and vasoactive intestinal peptide (VIP)
- Majority are “non-functional” – do not secrete, or secrete inactive proteins
- Prognosis dependent on stage, tumor differentiation and proliferative index
• Median survival for stage IV disease is about 70 months
• 5 year survival dependent on grade*
  • Low-grade (NET, grade 1) 75%
  • Intermediate grade (NET, grade 2) 62%
  • High-grade (NEC, grade 3) 7%
• Indication for treatment:
  • Pain
  • Symptoms from hormone secretion
  • High tumor burden
  • Progression of disease under observation
• Treatment options include: cytoreductive surgery, liver directed therapy, somatostatin analogues, anti-angiogenic agents, mTOR inhibitors, chemotherapy and PRRT

Introduction cont’d

• Treatment options include:
  • cytoreductive surgery
  • liver directed therapy
  • somatostatin analogues
  • anti-angiogenic agents
  • mTOR inhibitors
  • Chemotherapy
  • PRRT
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 panNETs 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
  • 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 midgut 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

- RADIANT 3\textsuperscript{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\textsuperscript{2}: 44 mos vs 37.7 mos (p =0.30); attributed to crossover design
  - Side effects: stomatitis, rash, diarrhea, fatigue 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 RECIST 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/thalidomide\(^1\): RR 45% (n=11)
  - Temozolomide/capecitabine\(^2\): retrospective, n=30
    - RR 70%; median PFS 18 mos; 2-year OS 92%
    - Correlation with MGMT expression
    - Heme toxicity
- ECOG 2211: tem/cape versus tem alone, closed to accrual


Chemotherapy cont’d

• **FOLFOX**
  - 31 patient receiving mFOLFOX6\(^1\)
    - PR 29%, SD 41%
    - Median PFS 14.1 mos
    - No difference in efficacy based on primary site (pancreatic vs extrapancreatic) or Ki67 index (< 5% vs 5-20%)

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% vs 12%; PFS 16.7 mos vs 14 mos (HR = 0.80)

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

- Yttrium-90
  - Phase II study\(^1\): \( ^{90} \text{Y-DOTATOC} \)
    - 39 pts with GI and pulmonary NETs
    - ORR 38%, 5% CR
  - MAURITIUS\(^2\) : \( ^{90} \text{Y-DOTA-lanreotide} \)
    - 154 pts
    - RR 14%; SD 41%

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

• Lu-177-DOTATATE
  • Netherlands Experience – ERASMUS MC\(^1\)
    • 1214 patients with GEP-NET and bronchial NETs
    • Dose-finding and safety study
    • PFS 29 months; OS 63 months
    • 360 patients with GEP-NETs

ERASMUS cont’d

Median overall survival
- Bronchus: 52 months (95% CI 49–55)
- Pancreas: 71 months (95% CI 56–86)
- Midgut: 60 months (95% CI 52–68)
- Unknown: 53 months (95% CI 44–62)

Cumulative survival (%)

<table>
<thead>
<tr>
<th></th>
<th>No at risk</th>
<th>Bronchus</th>
<th>Midgut</th>
<th>Pancreatic</th>
<th>Unknown</th>
</tr>
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<tbody>
<tr>
<td>Months</td>
<td>23</td>
<td>10</td>
<td>0</td>
<td>0</td>
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<tr>
<td>181</td>
<td>92</td>
<td>28</td>
<td>17</td>
<td>4</td>
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<tr>
<td>133</td>
<td>71</td>
<td></td>
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<tr>
<td>82</td>
<td>31</td>
<td></td>
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</tbody>
</table>

No at risk
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: Octreotide 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%

NETTER-1 cont’d

A) Progression-free Survival

- Progression-free Survival (% of patients)
- Months since Randomization
- No. at Risk
  - $^{177}\text{Lu-DOTATATE}$ group: 116, 97, 76, 59, 42, 28, 19, 12, 3, 2, 0
  - Control group: 113, 80, 47, 28, 17, 10, 4, 3, 1, 0

B) Overall Survival (Interim Analysis)

- Overall Survival (% of patients)
- Months since Randomization
- No. at Risk
  - $^{177}\text{Lu-DOTATATE}$ group: 116, 108, 96, 79, 64, 47, 31, 21, 8, 3, 0
  - Control group: 113, 103, 83, 64, 41, 32, 17, 5, 1, 0

\( P<0.001 \)
\( P=0.004 \)
### Table 4. Adverse Events (Safety Population)\(^a\)

<table>
<thead>
<tr>
<th>Event</th>
<th>(^{177})Lu-Dotatate Group (N = 311)</th>
<th>Control Group (N = 310)</th>
<th>P Value(^b)</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>
</tr>
<tr>
<td>Any adverse event</td>
<td>105 (41)</td>
<td>46 (41)</td>
<td>92 (44)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>65 (59)</td>
<td>4 (4)</td>
<td>13 (12)</td>
</tr>
<tr>
<td>Nausea</td>
<td>52 (47)</td>
<td>8 (7)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29 (26)</td>
<td>3 (3)</td>
<td>29 (26)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>32 (29)</td>
<td>3 (3)</td>
<td>21 (19)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (13)</td>
<td>0</td>
<td>15 (14)</td>
</tr>
<tr>
<td>General disorders</td>
<td>44 (40)</td>
<td>2 (2)</td>
<td>28 (25)</td>
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<tr>
<td>Fatigue or asthenia</td>
<td>16 (14)</td>
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<td>8 (7)</td>
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<tr>
<td>Edema peripheral</td>
<td>28 (25)</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Blood disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16 (14)</td>
<td>0</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>20 (18)</td>
<td>10 (9)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>11 (10)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6 (5)</td>
<td>1 (1)</td>
<td>1 (1)</td>
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<tr>
<td>Neutropenia</td>
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<tr>
<td>Musculoskeletal disorders</td>
<td>32 (29)</td>
<td>2 (2)</td>
<td>22 (20)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
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<tr>
<td>Nutrition disorders</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>
<td>0</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 (11)</td>
<td>0</td>
<td>6 (5)</td>
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<tr>
<td>Vascular disorders</td>
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<tr>
<td>Flushing</td>
<td>14 (13)</td>
<td>1 (1)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Skin disorders</td>
<td>12 (11)</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>12 (11)</td>
<td>0</td>
<td>6 (5)</td>
</tr>
</tbody>
</table>

\(^a\)P values are for comparisons between the \(^{177}\)Lu-Dotatate and placebo groups. \(^b\)P values are for comparisons between the \(^{177}\)Lu-Dotatate and placebo groups.
PRRT

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

Will be available at Yale in early Spring 2018
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

- Recognized therapies for metastatic pancreatic endocrine neoplasms
  - Observation
  - 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
Happy Hour starts now!!

- Thank you for your attention
- Have a great weekend.