What's New & Novel with Radionuclides & Neuroendocrine Neoplasms?

Disclosures

- I have nothing to disclose

Objectives

- Recognize the role of current anticancer therapies in the management of gastrointestinal neuroendocrine tumors (GEP-NET)
- Recognize the evolving use of theranostics within GEP-NET
- Describe the complexities and intricacies involved with lutetium-177 dotatate therapy

Audience Response Question #1

- Based on the response rates observed in clinical trials, a patient with advanced pancreas neuroendocrine tumor (PNET) experiencing tumor related pain would be more likely to achieve symptomatic relief from which of the following?
  - Somatostatin analogue (octreotide or lanreotide)
  - Everolimus
  - Sunitinib
  - Capecitabine/temozolomide

Audience Response Question #2

- Which of the following statements regarding theranostics in GIP-NET is FALSE?
  - Theranostics is a form of personalized medicine
  - Dotatate is a somatostatin analogue with higher receptor binding affinity compared to octreotide
  - Imaging with 111Lu-dotatate PET assists in determining treatment eligibility for 68Ga-dotatate therapy
  - Theranostics may assist in predicting risks for specific treatment related toxicities

Audience Response Question #3

- Which of the following statements regarding lutetium-177 dotatate therapy is FALSE?
  - An amino acid coinfusion is required for renal protection, and commercially available amino acids tend to be more emetogenic compared to compounded versions
  - Lutetium-177 dotatate is predominantly cleared renally, therefore, urinary contamination can be a concentrated source of radiation exposure
  - Results from NETTER-1 demonstrated a clinically and statistically significant improvement in both PFS and OS among patients treated with lutetium-177 dotatate
  - A patient with non-functional unresectable carcinoid should receive first line treatment with lutetium-177 dotatate based on its superiority over other options
Background: Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

- Incidence: 3.56 per 100,000 persons/year
- Prognosis depends on stage, histologic grade, & site of origin

Carcinoid Syndrome

- Symptoms
  - flushing
  - diarrhea
  - palpitations
  - bronchospasm
  - hypotension
- Frequency: 15%
- Mediators: Serotonin, 5-HT, histamine, prostaglandins, histamine

Antiproliferative Treatment Concepts

- Approaches vary depending on:
  - Disease status
  - Extent of metastases, symptomatic burden, & tempo of progression
  - Primary location of tumor
  - Histologic grade
  - Somatostatin receptor avidity
  - Hormonal activity of the tumor
  - Patient specific characteristics
- Systemic categories
  - Somatostatin analogues
  - Octreotide, lanreotide
  - Targeted therapy
    - everolimus, sunitinib, pazopanib
  - Peptide receptor radionuclide therapy (PRRT)
    - 177Lu-DOTATATE
  - Cytotoxic chemotherapy
    - Capecitabine + temozolomide,
      platinum + etoposide, streptozocin
  - Interferon

PROMID: Octreotide LAR

- Inoperable or metastatic midgut NETs (n=85)
- Treatment naïve
- Mixed functional status
- Karnofsky PS ≥ 60
- Exclusion criteria: anti somatostatin therapy, radiotherapy, chemotherapy

Primary endpoint
- OS
- QOL
- Biochemical response

Secondary endpoints
- OS
- QOL
- Biochemical response
PROMID: Octreotide LAR

- Responses
  - SD 67% vs 37% (p=0.0079)
  - PR 2% in each group
  - No CRs

- Active in both functional & non-functional tumors


CLARINET: Lanreotide Depot

Inoperable or metastatic GEP NETs (n=204)

- Somatostatin receptor +
- Ki-67 < 10%
- Non-functional tumors
- Mostly treatment naïve
- Karnofsky PS ≥ 60

- Lanreotide 120mg Q28D (n=101)
- Placebo (n=103)

1:1 Randomization

Primary endpoint
- PFS

Secondary endpoints
- OS
- QoL
- Biochemical response


RADIANT: Everolimus

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Treatment</th>
<th>Endpoints</th>
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</thead>
<tbody>
<tr>
<td>RADIANT-1</td>
<td>Open label phase II (n=160)</td>
<td>Advanced PNET w/ PD on chemo</td>
<td>Everolimus (+/- octreotide LAR)</td>
<td>P: ORR S: PFS, OS</td>
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<tr>
<td>RADIANT-2</td>
<td>Randomized, double-blind phase III (n=423)</td>
<td>Advanced NET w/ carcinoid symptoms</td>
<td>Octreotide LAR (+/- everolimus)</td>
<td>P: PFS S: OS, ORR, 5-HIAA, CgA</td>
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<tr>
<td>RADIANT-3</td>
<td>Randomized, double-blind phase III (n=352)</td>
<td>Advanced GI &amp; lung non-functional NET</td>
<td>Everolimus vs placebo</td>
<td>P: PFS S: OS, ORR</td>
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<td>RADIANT-4</td>
<td>Randomized, double-blind phase III (n=302)</td>
<td>Advanced GI &amp; lung non-functional NET</td>
<td>Everolimus vs placebo</td>
<td>P: PFS S: OS, ORR, CgA</td>
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Clinical Trials: Sunitinib

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<td>SUN-1111</td>
<td>Randomized, double-blind phase III (n=171)</td>
<td>Advanced mixed functional PNET</td>
<td>Sunitinib 37.5 mg/d vs placebo</td>
<td>PFS: 11.4 vs 5.5 m ORR: 9.3 vs 0%</td>
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**Alliance A021202: Pazopanib**

- **Advanced Carcinoid** (n=171)
  - G1 or G2
  - PD within last 12 months
  - Prior SSA required

<table>
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<tr>
<th>Arm</th>
<th>SD</th>
<th>ORR</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
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<td>Pazopanib 800 mg/day</td>
<td>96% vs 81% (p=0.001)</td>
<td>2 vs 8% (p value not reported)</td>
<td>11.6 vs 6.5 (HR=0.53; p=0.0005)</td>
<td>41 vs 42 (HR 1.13; p=0.7)</td>
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<tr>
<td>Placebo</td>
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Primary endpoint: PFS
Secondary endpoints: OS, CR, Safety

**Role of Cytotoxic Chemotherapy**

E2211: Capecitabine + Temozolomide

- **Advanced PNET** (n=144)
  - G1 or G2
  - PD within last 12 months
  - No prior chemotherapy

<table>
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<tr>
<th>Arm</th>
<th>T 100 mg/m² q28d days 1–5 (n=72)</th>
<th>C 750 mg/m² BID days 1–14 (n=72)</th>
<th>T 200 mg/m² q28d days 10–14 (n=72)</th>
</tr>
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</table>

Primary endpoint: PFS
Secondary endpoints: OS, RR

**Case #1**

- 48 y.o. M with G1 small bowel NET resected in 2007, new metastases in liver and mesenteric LN in 2015, + carcinoid syndrome
  - PMH includes stage 4 CKD
  - Octreotide LAR 7/2015 – present
  - PD on CT & 68Ga dotatate PET 5/2019

- What are his treatment options?
- How would you counsel & monitor?

**Audience Response Question #1**

- Based on the response rates observed in clinical trials, a patient with advanced PNET experiencing tumor related pain would be more likely to achieve symptomatic relief from which of the following?
  - Somatostatin analogue (octreotide or lanreotide)
  - Everolimus
  - Sunitinib
  - Capecitabine/temozolomide
**Role of Theranostics**


**Imaging: Past & Present**


**Background: 177Lu-Dotatate**

- FDA approved January 2018
- Granted priority review
- FDA indication
  - Treatment of somatostatin receptor-positive GEP-NETs including foregut, midgut, & hindgut NETs in adults
- Drug class
  - Peptide receptor radionuclide therapy (PRRT)
- Synonyms
  - (177Lu) Oxodotreotide
  - 177Lu-DOTA0-Tyr3-Octreotate


**Mechanism of Action: 177Lu-Dotatate**

https://seekingalpha.com/article/4124709-novartis-nvs-r-and-d-investor-presentation-slideshow

**Pharmacokinetics & Interactions: 177Lu-Dotatate**

- Terminal blood elimination half-life = 2.9 (± 0.06) days
- 177Lu radioactive decay half-life = 6.7 days
- Renal impairment
  - Predominantly cleared renally
  - Risk of toxicity may be higher in patients with mild-moderate impairment
  - Severe impairment (CrCl < 30 mL/min) was not studied
- Hepatic impairment
  - No adjustment recommended for mild-moderate impairment
  - Severe impairment (T. bili > 3 x ULN) was not studied
- Drug interactions
  - Avoid long-acting SSAs for 4 weeks prior & 4 hours after 177Lu-dotatate
  - Avoid short-acting SSAs for 24 hours prior


**Dosing: 177Lu-Dotatate**

- 177Lu-dotatate 7.4 GBq (200 mCi) every 8 weeks x 4 doses
- 77% of patients in trial were able to receive all 4 doses
- Dose adjustments for adverse events
  - Withhold dose & resume at 50% once resolved
  - Thrombocytopenia (grade 3-4)
  - Anemia & neutropenia (grade 3-4)
  - Renal or hepatic toxicity (recommendations vary)
- Premedication & concomitant medications
  - Antiemetics 1 hour prior
  - Amino acid infusion x 4 hours starting 30 minutes prior
  - Octreotide LAR 30mg 4-24 hours after


**Administration Considerations: ¹⁷⁷Lu-Dotatate**

- Follow currently adopted practices for IV administration of radiopharmaceuticals.

**LUTATHERA® (lutetium Lu 177 dotatate) [package insert]. Meldola, Italy: Advanced Accelerator Applications; 2018.**

**NETTER-1: ¹⁷⁷Lu-Dotatate**

**Primary Endpoint**

- PFS

**Secondary Endpoints**

- OS
- ORR
- Safety

**177Lu-Dotatate + Octreotide LAR (n=116) vs Octreotide LAR (n=113)**

**NETTER-1: Inoperable, Locally Advanced or Metastatic Midgut NETs (n=229)**

- Somatostatin receptor (+)
- Ki67 index ≤ 20%
- PD on octreotide LAR
- Karnofsky PS ≥ 60

**177Lu-Dotatate + Octreotide LAR (n=116)**

- L: 7.4 GBq Q8W x 4 ± 30mg Q4W

**Octreotide LAR (n=113)**

- 60mg Q4W


**ERASMUS: ¹⁷⁷Lu-Dotatate**

**Endpoints**

- PFS
- OS
- ORR
- Safety

**Bronchial & GEP-NETs (n=1214)**

- Somatostatin receptor (+)
- Karnofsky PS ≥ 50

**177Lu-Dotatate**

7.4 GBq Q6-13W x 4 ± Octreotide LAR


**PRRT: Shrinking is Possible**

Safety Profile

- Warnings/Precautions
  - Myelosuppression
  - Secondary malignancies (0.5-2.7%)
  - Renal toxicity
  - Requires amino acid co-infusion
  - Hepatotoxicity (<1%)
  - Neuroendocrine hormonal crisis (1%)
  - Embryo-fetal toxicity & infertility


Quality of Life Outcomes


Salvage PRRT

- Dutch retrospective study in patients with PD after initial PFS ≥18 months with I-PRRT or ≥14 months after R-PRRT (n=168) & RR-PRRT (n=13)
- Well tolerated
  - 2.2% MDS/AML
  - No grade III/IV nephrotoxicity


Cost Comparison

- 177Lu-dotatate
  - Patient assistance program is limited
  - Cancellation fee may be applied

PRRT Implementation & Planning

- FDA approval: 1/26/18
- 1st treatment administered: 4/18/18
- R&D approval: 2/20/18
- ≥120 pts on waitlist; ≥74 pts started; ≥180 doses administered 9/13/19

- PRRT
  - My role & responsibilities
    - Serve as a liaison between: Pharmacy, medical oncology, nuclear medicine, nursing, finance, radiation therapy, etc.
    - Maintain/update prescreening waitlist & treatment calendar
  - Multi-disciplinary decisions
    - Treatment location
    - Work flow
    - Amino acid solution
    - Split treatment days
    - IV access
    - Foley catheter
    - Scaling capability
    - Wartis management
    - PA process

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  - PA process

PRRT Controversies & Remaining Questions

- Exclusion of patients with bulky mesenteric disease?
- Which patients receive the most benefit with PRRT?
- What is the preferred sequence of therapy?
- Timing & selection of SSA with PRRT

- Exclusion Criteria
  - Creatinine (mg/dL) >40% increase > 1.7
  - Creatinine clearance (mL/min)* < 40 or 40% decrease < 50
  - Bilirubin > 3x ULN
  - Albumin (g/dL) + < 3 +

- *Cockcroft Gault with actual body weight
- **Treatment related toxicity, not baseline organ function
Case #2

- 71 y.o. F with G2 PNET dx in 2014 with metastases to liver, small bowel, para-aortic LN, & hilum
- Capecitabine/temozolomide 6/2016 – 11/2017
- Sunitinib 11/2017 – 2/2018
  - Grade 4 GIB
  - ¹⁷⁷Lu dotatate PET 5/2018
  - ¹⁷⁷Lu dotatate x 4 doses 5/2018 – 11/2018
  - Grade 1 fatigue & cytopenias
  - 30% decrease in tumor volume – PR by RECIST
- Maintenance octreotide LAR as of 7/2019

Audience Response Question #2

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Recent Pertinent Negative Data

- Phase II basket study included 107 patients with well- and moderately-differentiated NET who received pembrolizumab after PD on ≥ 1 prior therapy
  - 3.7% ORR (only in PDL-1 negative tumors)
  - 4.1 month PFS
- Retrospective study in 4,892 patients with stage I-III PNET comparing perioperative therapy vs. surgery alone
  - Shorter OS with perioperative therapy (HR 1.45, p=0.006)

Treatment Overview

  - Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)
- NCCN Guidelines Index: Targeted Therapies (Pembrolizumab)
  - Pembrolizumab (Keytruda®)
  - Pembrolizumab in the Treatment of Advanced or Metastatic Neuroendocrine Tumors
- Pembrolizumab (Keytruda®) is indicated for the treatment of adults with unresectable progressive small cell lung cancer
  - Pembrolizumab (Keytruda®) in combination with axitinib (Inhibitor of the VEGF Receptor Tyrosine Kinases)
  - Pembrolizumab (Keytruda®) in combination with apatinib (Inhibitor of the VEGF Receptor Tyrosine Kinases)
Future Directions

<table>
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<tr>
<th>Treatment</th>
<th>Phase</th>
<th>Patient Population</th>
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</thead>
<tbody>
<tr>
<td>111Lu-dotatate</td>
<td>II</td>
<td>Inoperable Pheochromocytoma/Paraganglioma</td>
</tr>
<tr>
<td>Nivolumab + 177Lu-dotatate</td>
<td>I/II</td>
<td>Extensive Stage Small Cell Lung Cancer</td>
</tr>
<tr>
<td>Sunstimab vs. 177Lu-dotatate</td>
<td>II</td>
<td>Advanced PMT</td>
</tr>
<tr>
<td>Everolimus vs. 177Lu-dotatate</td>
<td>II</td>
<td>Advanced GEP-NETs</td>
</tr>
<tr>
<td>Pazopanib + temozolomide</td>
<td>II</td>
<td>Advanced PMT</td>
</tr>
<tr>
<td>PEG-221 (SSA-ZM1 conjugate)</td>
<td>II</td>
<td>Advanced GEP or lung NETs</td>
</tr>
<tr>
<td>Cabozantinib vs. placebo</td>
<td>II</td>
<td>Advanced GEP or lung NETs after PD on everolimus</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>II</td>
<td>Advanced NET after PD on initial therapy</td>
</tr>
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Conclusions

- SSAs, everolimus, sunitinib, pazopanib, capetcitabine/temozolomide, & PRRT demonstrate anti-proliferative properties & play a significant role in the treatment of patients with advanced GEP-NETs.
- 177Lu-dotatate & 186Re-dotatate are a revolutionary therapeutic pair, however, candidate selection & timing are important considerations.
- Implementation & coordination of a 177Lu-dotatate program is a challenge & requires multidisciplinary strategic planning.

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Sources Cited

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https://www.clinicaltrials.gov