Theranostics in Neuroendocrine Tumors

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University of Bonn
The theranostics approach in nuclear medicine couples diagnostic imaging and therapy with the same, but differently radiolabeled, molecule, or the same agent in different dosages.

The aim of Theranostics is to provide the right therapy for the right patient at the right time.
Radioiodine diagnostic and therapy
NET overexpression of the somatostatin receptors

- Enhanced expression of SSTR on NET compared to normal tissues
- Binding of the SSTR-radiologands to the cell surface
- Internalisation of the SSTR-radiologand-complex
- Uptake of SSTR-radioligand from other cells within the Tumor (such as endothelial cells)
NET overexpression of the somatostatin receptors

- 5 subtypes (SSTR1-5)
- SSTR2 most commonly expressed
- Natural ligand: somatostatin

(SSTR1,3,4)

Immunohistochemical staining of the somatostatin receptor of a NET (brown)

With courtesy to Dr. Florian Gaertner (University Hospital Bonn)
Theranostics in Neuroendocrine Neoplasia

68Ga-DOTATOC PET

177Lu-DOTATATE

Theranostics
Theranostics in Neuroendocrine Tumors

Topics

- Neuroendocrine neoplasia (NEN)
- New WHO classification of NEN
- Imaging using radionuclides
- PRRT
  - Evidence
  - Toxicity
  - Combination therapies
Neuroendocrine Neoplasia

- Pituitary
- Medullary thyroid cancer
- Thymus-NET
- Neuroblastoma and pheochromocytoma
- Carcinoids of the urogenital tract

Pulmonary NEN
- Bronchus-NET
- Typical and atypical
  - SCLC
  - LCNEC

(GEP-NEN):
- stomach,
- Duodenum,
- pancreas,
- jejunum,
- ileum,
- appendix,
- Colon and rectum

Tumors of the peripheral nervous system
- schwannoma
- paraganglioma
- neuroblastoma

Merkel cell carcinoma of the skin
75% of all neuroendocrine tumors are in the GEP region.

Small intestinal neuroendocrine tumors were first distinguished from other tumors in 1907 by Siegfried Oberndorfer.

They were named carcinoid tumors because their slow growth was considered to be "cancer-like" rather than truly cancerous.

(Karzinoide Tumoren des Dünndarmes. Frankfurter Zeitschrift für Pathologie, 1907, 1: 426–429)
Incidence of GEP-NEN

Figure 1. Incidence Trends of Neuroendocrine Tumors (NETs) From 1973 to 2012

Dasari et al., JAMA Oncology 2017
Symptoms

- Behavior: indolent (slow growing) to aggressive
- Symptoms: often non-specific, often late in advanced stages

Vinik AI et al. Pancreas 2009;38:876-889
Small primary and metastases
<table>
<thead>
<tr>
<th>Histological differentiation</th>
<th>WHO-/ENETS- Grade (2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Well-differentiated</strong></td>
<td></td>
</tr>
<tr>
<td>Low grade:</td>
<td></td>
</tr>
<tr>
<td>Intermediate grade:</td>
<td>G1-NET</td>
</tr>
<tr>
<td>Ki-67 ≤ 3%</td>
<td></td>
</tr>
<tr>
<td>High grade:</td>
<td>G2-NET</td>
</tr>
<tr>
<td>Ki-67 &gt; 3% &lt; Ki-67 ≤ 20%</td>
<td></td>
</tr>
<tr>
<td><strong>Poorly-differentiated</strong></td>
<td></td>
</tr>
<tr>
<td>High grade:</td>
<td>G3-NET</td>
</tr>
<tr>
<td>Ki-67 &gt; 20%</td>
<td></td>
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<tr>
<td></td>
<td>Small cell type</td>
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## NEN classification according to histopathology

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</tr>
<tr>
<td>Ki-67 ≤ 3%</td>
<td>SSTR PET</td>
</tr>
<tr>
<td>Intermediate grade:</td>
<td>G2-NET</td>
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<tr>
<td>3% &lt; Ki-67 ≤ 20%</td>
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</tr>
<tr>
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PET & SPECT Tracers for the detection of NEN

- **111**In-Octreotid (OctreoScan®)
  - Available since 1989
  - Planar Scintigraphy / SPECT
  - Low sensitivity, long protocol (2 days), relatively high radiation exposure

- **68**Ga-DOTA-TOC / -NOC / -TATE
  - PET tracers
  - Higher sensitivity, higher resolution
  - Shorter protocols (2 hours), lower radiation exposure
PET & SPECT Tracers
SSTR-Imaging

$^{68}$Ga-DOTATOC PET/CT
limited availability
Investigation time: < 2 h
Radiation exposure: 3 mSv

$^{111}$In-Octreotide
Investigation time > 24 h
Radiation exposure: 9 mSv

Sensitivity 97%  
Sensitivity 65%
SSTR-PET

Indications

- Staging
  - Metastasis detection / exclusion
  - Primary tumor localization

- Re-Staging
  - Tumor residuals
  - Recurrence

- Determination of receptor status
  - Biotherapy
  - PRRT

- Therapy-Monitoring
• **Staging**
  - SSTR PET "method of choice"
  - should generally be used in all patients preoperatively for staging
  - Exception: insulinomas, since sensitivity is only about 25%

• **Follow-Up**
  - **G1 > 2 cm, limited to pancreas, N0:**
    - US/CT/MR 6 - 12 months post-op, then annually
    - SSTR PET at diagnosis, then every 2 years
  - **G2 > 2 cm or locally invasive or N1:**
    - US/CT/MR every 3 months post-op
    - SSTR PET 3 months post-op, then annually

• **Zollinger-Ellison Syndrome:**
  - SSTR PET preoperatively recommended for gastrinoma localization (duodenum)

• **MEN1-Syndrome without detectable tumor:**
  - Routine use of SSTR PET still unclear
## NEN classification according to histopathology

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<td>G2-NET 3% &lt; Ki-67 ≤ 20%</td>
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SSTR PET: Small Invasive Tumour Radiolabel PET
FDG PET: Fluorodeoxyglucose PET
Indications for FDG PET

- Poorly differentiated neuroendocrine carcinomas (NEC G3)
- Evaluation of dedifferentiated tumor cells in NET G1 / G2 /G3
Scan instead of Biopsy?

Ileum NET, G1 (<2% MIB-1)

With courtesy to Prof. Dr. Kristiansen, Department of Pathology, University Hospital Bonn
FDG PET + SSTR PET

Therapy planning

CUP-NET, Ki67: 17%

P-NET, Ki67: 1-10%

P-NET, Ki67: 10-15%
P-NET Ki67: 5%

• <55% less responsive to platinum based chemo

• >55% more responsive (but still recurred quicker and worse survival)

**Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study**


1Department of Oncology, Haugesund University Hospital, Bergen, Norway; 2Department of Medical Sciences, Uppsala University, Uppsala, Sweden; 3Department of Surgery, Frederiksborg Hospital, Fredensborg, Denmark; 4Department of Oncology, University Francois Rabelais, Tours, France; 5Department of Gastroenterology, Odense University Hospital, Odense, Denmark; 6Department of Cardiology, Odense University Hospital, Odense, Denmark; 7Department of Oncology, University Hospital, Aarhus, Denmark; 8Department of Oncology, Aalborg University Hospital, Aalborg, Denmark; 9Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; 10Department of Oncology, Copenhagen University Hospital, Copenhagen, Denmark; 11Department of Oncology, Copenhagen University Hospital, Copenhagen, Denmark; 12Department of Haematology, Copenhagen University Hospital, Copenhagen, Denmark; 13Department of Surgery, Aarhus University Hospital, Aarhus, Denmark; 14Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; 15Department of Oncology, Odense University Hospital, Odense, Denmark; 16Department of Oncology, Odense University Hospital, Odense, Denmark; 17Department of Oncology, Odense University Hospital, Odense, Denmark; 18Department of Oncology, Odense University Hospital, Odense, Denmark; 19Department of Oncology, Odense University Hospital, Odense, Denmark; 20Department of Oncology, Odense University Hospital, Odense, Denmark; 21Department of Oncology, Odense University Hospital, Odense, Denmark.
**Indications for FDG PET**
- Poorly differentiated neuroendocrine carcinomas (NEC G3)
- Evaluation of dedifferentiated tumor cells in NET G1 / G2 / G3

**What is the frequency of FDG-positive scans in G1/G2 NET?**

13 % - 70 %

**What is the impact of FDG-positive scans on prognosis in G1/G2 NET?**

FDG-positivity is a significant prognostic factor

PET imaging in NEN
FDG PET + SSTR PET

different ways to treat
GEP-NEN Therapies

- OP
- RTX
- TACE/TARE
- Targeted Therapy
- Bio-TX
- PRRT
<table>
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<tr>
<th>Radionuclides</th>
<th>half time</th>
<th>$E_\beta$ [keV]</th>
<th>Distance [mm]</th>
<th>$E_\gamma$ [keV]</th>
<th>Pro/Cons</th>
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<td></td>
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<td>max</td>
<td>mean</td>
<td>max</td>
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<td>$^{90}$Y</td>
<td>2.7 d</td>
<td>935</td>
<td>2270</td>
<td>4</td>
<td>11,3</td>
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<td></td>
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</tr>
<tr>
<td>$^{177}$Lu</td>
<td>6.7 d</td>
<td>149</td>
<td>497</td>
<td>0.5</td>
<td>1,6</td>
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</table>

The table provides information on the half-life, mean and maximum energies of beta radiation, distance of emission, mean and maximum energies of gamma radiation, and a brief description of the pros and cons for each radionuclide. For $^{90}$Y, the pros include cross-fire and the cons include toxicity. For $^{177}$Lu, the energy values are given as 208 and 113 keV, labeled as 'Best therapeutic.'
Radionuclide Therapy of NEN using $^{177}$Lu-DOTATATE

**NETTER 1 - study**

G1 and G2 MIDGUT-NET, progressive under biotherapy, in each arm 115 patients

- **PRRT + Octreotide LAR 30mg**
  - PFS (median): not reached
- **Octreotide LAR 60mg**
  - PFS (median): 8.4 months
  - HR [95% CI]: 0.209 [0.129 – 0.338]
  - $p < 0.0001$

- **Overall survival**

FDA News Release

FDA approves new treatment for certain digestive tract cancers

For Immediate Release

January 26, 2018

The U.S. Food and Drug Administration today approved Lutathera (lutetium Lu 177 dotatate) for the treatment of a type of cancer that affects the pancreas or gastrointestinal tract called gastrointestinal neuroendocrine tumors (GEP-NETs). This is the first time a radioactive drug, or radiopharmaceutical, has been approved for the treatment of GEP-NETs. Lutathera is indicated for adult patients with somatostatin receptor-positive GEP-NETs.

“GEP-NETs are a rare group of cancers with limited treatment options after initial therapy fails to keep the cancer from growing,” said Richard Pazdur, M.D., director of the FDA’s Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA’s Center for Drug Evaluation and Research. “This approval provides another treatment choice for patients with these rare cancers. It also demonstrates how the FDA may consider data from therapies
Treatment With the Radiolabeled Somatostatin Analog 
$^{177}$Lu-DOTA$^0$,Tyr$^3$]Octreotate: Toxicity, Efficacy, and Survival

Dik J. Kwekkeboom, Wouter W. de Herder, Boen L. Kam, Casper H. van Eijck, Martijn van Essen, Peter P. Kooij, Richard A. Feelders, Maarten O. van Aken, and Eric P. Krenning

ABSTRACT

Patients and Methods
Patients were treated up to a cumulative dose of 750 to 800 mCi (27.8-29.6 GBq), usually in four treatment cycles, with treatment intervals of 6 to 10 weeks. Toxicity analysis was done in 504 patients, and efficacy analysis in 310 patients.

Results
An overall complete response rate 6 to 48 weeks after 0.8% of administrations. Complete and partial response rates were 2% and 28%, respectively. Minor responses were observed in 16% of patients, stable disease in 35%, and progressive disease in 20%.

- Better responses in pancreatic NETs than carcinoids
- Disease-specific survival:
  - 11 months for progressive disease
  - >48 months for stable disease or remission
- Global survival gain estimate: 23-69 months (vs. historical controls)
<table>
<thead>
<tr>
<th>Paper</th>
<th>Year</th>
<th>Type*</th>
<th>Radioligand</th>
<th>n</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
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<tr>
<td>Kwekkeboom J Clin Oncol</td>
<td>2008</td>
<td>RS</td>
<td>$^{177}$Lu-DOTATATE</td>
<td>188</td>
<td>23</td>
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<td>NA (≈46)</td>
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<td></td>
<td></td>
<td></td>
<td>all with refractory</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td>carcinoid syndrome</td>
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<td>41</td>
<td>22</td>
<td>88</td>
<td>27</td>
<td>43</td>
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</tbody>
</table>
Patient with Midgut NET, progressive under bio-therapy, Ki67: 5 %
Case example

Patient with Midgut NET, progress under bio-therapy

03/2014  1. Lu-DOTATATE Therapy with 6.0 GBq
06/2014  2. Lu-DOTATATE Therapy with 6.6 GBq
09/2014  3. Lu-DOTATATE Therapy with 6.7 GBq
12/2014  4. Lu-DOTATATE Therapy with 6.0 GBq
Case example
<table>
<thead>
<tr>
<th>Paper</th>
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<th>Type</th>
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<th>n</th>
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<th>PFS (mo)</th>
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<td>$^{177}$Lu-DOTATATE</td>
<td>26 (FD)</td>
<td>39</td>
<td>85</td>
<td>29+</td>
<td>NR</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>26 (RD)</td>
<td>18</td>
<td>77</td>
<td>20</td>
<td>NR</td>
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<td>68</td>
<td>60</td>
<td>85</td>
<td>34</td>
<td>53</td>
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</tbody>
</table>
Toxicities

- **Nephrotoxicity**
  - $^{177}$Lu-based PRRT: < 2 % (3-4° CTCAE)
  - $^{90}$Y-based PRRT: 5-10 % (3-4° CTCAE)

- **Hematotoxicity (reversible)**
  - $^{177}$Lu-based PRRT: 5-10 % (3-4° CTCAE)
  - $^{90}$Y-based PRRT: 8-13 % (3-4° CTCAE)

- **Late MDS**
  - 0.5-1%
Improving quality of life in patients with pancreatic neuroendocrine tumor following peptide receptor radionuclide therapy assessed by EORTC QLQ-C30

Milka Marinova1 · Martin Mücke2,3,4 · Lukas Mahlberg5 · Markus Essler5 · Henning Cuhls2 · Lukas Radbruch2 · Rupert Conrad6 · Hojjat Ahmadzadehfar5

Excluded from the analysis
n=63

- 47 patients did not fill the EORTC QLQ-C30 questionnaire or the form was incomplete
- 11 patients were missed to FU6 or less than 3-months FU
- 5 patients were still under PRRT therapy

Eligibility for the analysis
n=68

PRRT between 2007-2015 in P-NET
n=131

*European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [0-100]
IMPROVED QUALITY OF LIFE: P-NET under PRRT

Marinova et al. EJNMMI 2017
PRRT
mono- or combination therapy

PRRT as monotherapy
or in combination with biotherapy

PRRT + Temozolomide
PRRT + Temozolomide /Capecitabine

18F-FDG PET 68Ga-DOTATOC PET
18F-FDG PET 68Ga-DOTATOC PET
18F-FDG PET

18F-FDG PET 68Ga-DOTATOC PET 68Ga-DOTATOC PET 18F-FDG PET
Is there a survival benefit of adding SSA to PRRT as a combination therapy or maintenance therapy?
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All pts n (%)</th>
<th>Group 1 n (%)</th>
<th>Group 2 n (%)</th>
<th>(P(\chi^2))</th>
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</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>Male</td>
<td>89 (53.0)</td>
<td>40 (49.4)</td>
<td>49 (56.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Female</td>
<td>79 (47.0)</td>
<td>41 (50.6)</td>
<td>38 (43.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Age</strong></td>
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<td>n.s.</td>
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<tr>
<td>Mean</td>
<td>63.1</td>
<td>63.1</td>
<td>63.1</td>
<td>n.s.</td>
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<tr>
<td>Patients &lt;65</td>
<td>92 (54.8)</td>
<td>43 (53.1)</td>
<td>49 (56.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Patients &gt;65</td>
<td>76 (45.2)</td>
<td>38 (46.9)</td>
<td>38 (43.7)</td>
<td>n.s.</td>
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<tr>
<td><strong>EGOG-index</strong></td>
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<td></td>
<td></td>
<td>n.s.</td>
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<td>Median</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>n.s.</td>
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<tr>
<td>ECOG 0</td>
<td>34 (20.2)</td>
<td>11 (13.6)</td>
<td>23 (26.4)</td>
<td>n.s.</td>
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<tr>
<td>ECOG 1</td>
<td>114 (67.9)</td>
<td>60 (74.1)</td>
<td>54 (62.1)</td>
<td>n.s.</td>
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<tr>
<td>ECOG 2</td>
<td>20 (11.9)</td>
<td>10 (12.3)</td>
<td>10 (11.5)</td>
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<td><strong>Type of GEP-NET</strong></td>
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<td>n.s.</td>
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<td>84 (50)</td>
<td>48 (59.3)</td>
<td>36 (41.4)</td>
<td>n.s.</td>
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<td>46 (27.4)</td>
<td>18 (22.2)</td>
<td>28 (32.2)</td>
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<td>Others</td>
<td>38 (22.6)</td>
<td>15 (18.5)</td>
<td>23 (26.4)</td>
<td>n.s.</td>
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<td><strong>Tumor functionality</strong></td>
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<td>n.s.</td>
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<td>Functioning</td>
<td>99 (58.9)</td>
<td>44 (54.3)</td>
<td>55 (63.2)</td>
<td>n.s.</td>
</tr>
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<td>Nonfunctioning</td>
<td>69 (41.1)</td>
<td>37 (45.7)</td>
<td>32 (36.8)</td>
<td>n.s.</td>
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<td><strong>Ki67</strong></td>
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<td></td>
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<td>n.s.</td>
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<td>Mean</td>
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<td>5.8</td>
<td>5.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>113 (76.9)</td>
<td>54 (76.1)</td>
<td>59 (77.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>≥10 to ≤20%</td>
<td>34 (23.1)</td>
<td>17 (23.9)</td>
<td>17 (22.4)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
PRRT + Biotherapy

GEP-NET Therapies

PRRT + Chemotherapy

OP
CTX
RTX
TACE/TARE
Bio-TX
Targeted Therapy
1- Radiosensitizing 5-FU is administered as a continuous infusion at a dose of 200 mg/m²/day from the second cycle of PRRT starting 4 days prior to radionuclide administration and continuing for up to 3 weeks.

*During the period of this study, 5-FU is omitted from the first cycle to minimize flare as a result of hormone secretion*

2- Chemotherapy with oral 1,650 mg/m² capecitabine (Xeloda, Roche Products) for 14 consecutive days is commenced on the morning of radionuclide therapy. Cycles of capecitabine are repeated every 8 weeks at the time of each subsequent radiopeptide infusion.

3- Chemotherapy commences 5 days prior to PRRT with oral capecitabine 1,650 mg/m² for 14 days in patients not receiving temozolomide. The capecitabine dose is fixed at 1,500 mg/m² for 14 days in all patients receiving temozolomide. Oral temozolomide is given in the last 5 days of each 14-day capecitabine period.
PRRT+Chemo (PRcRT)


median OS: was not achieved

Later reported: median OS: 55 months

median PFS: 48 months

Safety:

Leucopenia: in 42 % (no G3/4)

Anemia: 38 % (no G3/4)

Thrombocytopenia: in 38 % (G3/4: 6%)

we need more data


P-NET G2 (Ki67: 4 %) 2015

Biotherapy
3 cycles
PRRT
P-NET G2 (Ki67: 4 %) 2015
Ki67: 60 % (2018)
P-NET G2 (Ki67: 4 %) 2015

Ki67: 60 % (2018)

07/2017 08/2017 06/2018 06/2018

3 cycles PRRT with chemo
Take-home message

- Both SSTR PET and FDG PET are important modalities in NEN
  - Treatment Planning / Biopsy
- PRRT is one of the most efficacious systemic therapies for inoperable NETS
  - Objective response
  - PFS and OS
  - Quality of life
- PRRT is well tolerated
  - Serious toxicity is rare with $^{177}$Lu-DOTATATE
PRRT is an essential modality in the multidisciplinary management of NET patients

PRRT may be combined with biotherapy

PRRT should be combined with chemotherapy in specific cases
Thank you for your attention!

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