ESMO ADVANCED COURSE ON
Individualising the therapeutic approach in patients with NENs: Peptide Receptor Radionuclide Therapy (PRRT)

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DISCLOSURES

Consulting or Advisory Role | Therasphere, AAA, AML

Speakers’ Bureau | PrimeOncology, Therasphere, AAA, Jansen
Acknowledgements

- The Christie
- Nuclear Medicine/ CMPE department
- Department of Radiology
- ENETs NET team
Why, what and when: Factors that dictate NEN management and imaging

1. Grade
2. Primary
3. Liver only
4. Functional
5. Progressive
6. Therapy options: PRRT?

Management led by specialist NEN MDT
Molecular Imaging

“Molecular imaging is aimed at the exploitation of specific molecules as the source of image contrast”

Aims:

• Earlier detection and characterization of disease ("molecular signature" prior to irreversible damage)

• Understanding of underlying biology

• Selection of specific treatment option for targeted therapy

• Concept of THERANOSTICS nuclear medicine/molecular imaging ideally set for this dual role
Theranostics- Therapy and Diagnostics

*Theranostics* publishes innovative research articles reflecting the fields of *in vitro* diagnostics and prognostics, *in vivo* molecular imaging, molecular therapeutics, image-guided therapy, biosensors, system biology and translational medicine, personalized medicine and a broad spectrum of biomedical research that can be applied to future theranostic applications.
Radionuclide Tracer

Key aspect of nuclear medicine imaging- labelled radiotracers

Octreotide is a somatostatin analogue
If we can see it, we can treat it!

Principles of Nuclear imaging and therapy (Theranostics)
Results:

- $^{68}$Ga-PET imaging changed management in 36 patients (70.6%), who were subsequently deemed suitable for peptide receptor–targeted therapy

Conclusion:

- In patients with negative or equivocal $^{111}$In-DTPA-octreotide findings, $^{68}$Ga-DOTATATE PET identifies additional lesions and may alter management in most cases

PRRT – What is the evidence?
**NETTER -1 Study Objectives and Design**

**Aim**
Evaluate the efficacy and safety of $^{177}$Lu-Dotatate + SSAs (symptoms control) compared to Octreotide LAR 60mg (off-label use)\(^1\) in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use).

**Design**

**Treatment and Assessments**
Progression free survival (RECIST criteria) every 12 weeks.

**Baseline and Randomization**
- $n = 115$
- 4 administrations of 7.4 GBq of $^{177}$Lu-Dotatate every 8 weeks + SSAs (symptoms control)

**5 Years follow up**
- Octreotide LAR (high dose - 60mg every 4 weeks\(^1\))

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\(^1\) FDA and EMA recommendation
Progression-Free Survival

N = 229 (ITT)
Number of events: 91
$^{177}\text{Lu}$-Dotatate: 23
Oct 60 mg LAR: 68

Estimated Median PFS in the $^{177}\text{Lu}$-DOTATATE arm
$\approx 40$ months

Hazard ratio: 0.21
[0.13 – 0.33]
$p < 0.0001$

79% reduction in the risk of disease progression/death

All progressions centrally confirmed and independently reviewed for eligibility (SAP)
Overall Survival (interim analysis)

N = 229 (ITT)
Number of deaths: 40

\(^{177}\)Lu-Dotatate: 14
Oct 60 mg LAR: 26

Hazard ratio: **0.398**
[0.21 – 0.77]
P = **0.0043**

All cases independently reviewed for eligibility (SAP)

*Prespecified interim analysis significance level p<0.000085*
NETTER-1: Effects of quality of life

Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With $^{177}$Lu-Dotatate in the Phase III NETTER-1 Trial

Jonathan Strosberg, Edward Wolin, Beth Chasan, Matthew Kulke, David Bushnell, Martyn Caplin, Richard P. Baum, Pamela Kruz, Timothy Holsday, Andrew Heidtman, Kjell Olberg, Maribel Loper& Sierra, Thomas Thevenet, Ines Margalet, Philippe Ruszniewski, and Eric Kremmling, on behalf of the NETTER-1 Study Group

Results
TTD was significantly longer in the $^{177}$Lu-Dotatate arm ($n = 117$) versus the control arm ($n = 114$) for the following domains: global health status (hazard ratio [HR], 0.406), physical functioning (HR, 0.518), role functioning (HR, 0.580), fatigue (HR, 0.621), pain (HR, 0.566), diarrhea (HR, 0.473), disease-related worries (HR, 0.572), and body image (HR, 0.425). Differences in median TTD were clinically significant in several domains: 28.8 months versus 6.1 months for global health status, and 25.2 months versus 11.5 months for physical functioning.

Conclusion
This analysis from the NETTER-1 phase III study demonstrates that, in addition to improving progression-free survival, $^{177}$Lu-Dotatate provides a significant QoL benefit for patients with progressive midgut NETs compared with high-dose octreotide.

J Clin Oncol 36:2578-2584. © 2018 by American Society of Clinical Oncology
NETTER-1

- Compelling evidence for PRRT in NET grade 1 and 2 patients
- RCT evidence based and fulfils the Theranostic principles
How does PRRT work?

A form of ‘hybrid’ therapeutics

Partly ‘pharmaceutical’ principles- IV injection of tracer in suitable patients based on a biomarker test utilising a specific diagnostic test

Partly ‘radiotherapy’ principles- hence the complexity of the technique

Hence why it has been poorly developed thus far
Radio-immunotherapy & Radionuclide therapy

First steps in the realisation of targeted ‘magic bullet’ and synergistic radiation cancer therapy

**Concept**

Immunoglobin/ receptor ligand  

Beta- emitting radionuclide

Targeted cancer cell
*BEXXAR*: Radioisotope iodine 131 linked to a chimeric monoclonal antibody against CD20 antigen
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<th>$\gamma$</th>
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Indications for PRRT in GEP NEN

As per NICE guidance 2018 Lutetium (177Lu) oxodotreotide (Lutathera, AAA, referred to as lutetium) is indicated for:

- ‘Unresectable’ or metastatic
- Progressive- symptomatic, morphological
- Well-differentiated (G1 and G2)
- Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP NETs) in adults'.
Suitable Patients

- Tumour uptake on the SSTR PET-CT scan should be at least as high as normal liver uptake. Comparable uptake with other somatostatin receptor imaging modalities may apply, but direct correlations are not available.
- The patient should have inoperable disease.
- Life expectancy at least 3–6 months.
- Tumour differentiation grade 1 or 2.
- Tumour proliferation rate, with a Ki-67/mitotic index<20%.
Patient relative contraindications (case by case assessment of patients)

- The following parameters are relative contra-indications (as modified from the NETTER-1 study) apart from pregnancy or breast feeding (unless discontinued) which are an absolute contraindication:
  - Eastern Cooperative Oncology Group (ECOG) performance status 3

- Severe myelosuppression (as indicated by any of the following):
  - Hb <5 mmol/L,
  - WBC <2 ×10^9 /L,
  - Neutrophils <1.5×10^9 /L,
  - RBC <3×10^9 /L,
  - Platelets <75×10^9/L
Patient relative contraindications (case by case assessment of patients)

- Severe liver or renal failure (as indicated by any of the following):
  - eGFR < 50,
  - bilirubin > 3 x upper limit of normal,
  - albumin < 30 g/L and prothrombin time increased.
- Severe cardiac impairment.
- Unstable patient condition, not allowing isolation therapy.
- Previous myelotoxic chemotherapy or extended external bean irradiation fields to the bone marrow (pelvis, spine). In doubtful cases of haemato logical compromise a bone marrow biopsy might be indicated.
- Persisting depressed platelets values following prior PRRT cycles can impede the timing and dosing of subsequent cycles.
Things to be aware of

- Clinical assessment by medical oncology/endocrinology team

- Pre-treatment diagnostic imaging must be within 4-12 weeks of start of therapy.

- Check the medication of the patient for drugs which may interfere with the uptake and/or retention of somatostatin analogues (lots of possible interactions).

- For patients receiving long acting somatostatin analogue formulations treatment should be scheduled at the nadir of the pharmacological activity, usually at day 21-28 following the previous injection. Patients should be switched to short acting formulations up to 1 day before PRRT if symptom control is required.
How PRRT is done

- Infusion of amino acid solutions that contain lysine and arginine is essential to reduce kidney radiation absorbed dose. A solution of 2.5% lysine, 2.5% arginine in 1 litre saline (or commercial alternative) can be infused in 4 hours, starting 30 min before the administration of the radiopharmaceutical.

- Before beginning the amino acid infusion, appropriate measures against nausea and vomiting should be undertaken by administering an antiemetic (e.g. 5-HT3 antagonist, such as granisetron or odansetron) and/or a corticosteroid (e.g. dexamethasone). Further antiemetics may be administered PRN.

- Nutrition and fluid intake should be similar to the pre-treatment tracer study. Adequate hydration must be ensured.

- Encourage bladder emptying hourly for the first 12 hours. If patient cooperation with fluid intake or kidney function is an issue, an overnight infusion of IV saline can be administered.

- A resuscitation cart as well as a trained emergency team must be available.
What dose and utility of ‘Dosimetry’?

- Controversial

- NETTER-1 did not perform routine dosimetry on all patients

- Currently the recommended dose of Lu177 DOTATATE is 7.4 GBq x 4 doses 8-10 weeks apart
Post PRRT follow up/toxicity

- All patients receive whole body planar imaging at 24 hours post therapy

- Blood test monitoring every two weeks (until the next PRRT cycle, or for 12 weeks following the final cycle) and NET clinic follow up 6 weeks following treatment will be organised by the nuclear medicine team

- Follow up scans should be performed at mid cycle (after 2 cycles) and 12 weeks post final therapy.

- Long term clinical and blood parameter follow up to assess delayed renal toxicity and/or myelosuppression.
Repeat Cases to emphasise the principles of Theranostics
Case 1- 60 yr male

1. Grade
2. Primary SB
3. Liver only Not involved
4. Functional No
5. Progressive No
6. PRRT? ? Future

Theranostic option of choice= Radical curative surgery
## Case 2 - 46 yr female

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<td>4. Functional</td>
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<td>5. Progressive</td>
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<tr>
<td>6. PRRT?</td>
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Theranostic option of choice = PRRT

![68Ga DOTATOC](image)

177Lu DOTATATE
# Case 3- 15 yr female

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- **Theranostic option of choice= Chemotherapy (cis-etop)**

- **68Ga DOTATOC**
- **18 FDG**
Current status of Ga68 DOTA SSTR imaging and PRRT in England

- Ga68 DOTA SSTR PET CT will be commissioned in NC2 PET CT wave
- PRRT for NET approved by NICE in 2018
- Utility is based on NETTER-1
- Only progressive GEP NET grades 1 and 2
- No second treatments
- Treatment centres are in the process of being commissioned
- 2 significant developments underpinned by clinical trials and licensed Theranostic tracers
Future
Concept of “mitotically-active” disease- where do the tracers fit?

Principles to aid decision-making

- Concept of “mitotically-active” disease
- Patients usually live long enough to receive multiple therapies
- Need to identify sub-groups of patients (through research) who benefit most from each therapy
- One-size does not fit all
Future: PRRT for G3/Combination/ NEN Theranostic driven treatment

- Future clinical trials
- Lots of exciting opportunities
Somatostatin receptors part of G protein sub group- **Antagonist** tracers

Somatostatin Receptor Antagonists for Imaging and Therapy  
Summary

- Theranostic utilises molecular imaging as a biomarker signal to manage patients
- Specialist pathology / imaging assessment guides the entire management pathway - G1, G2, G3a/b
- Molecular Imaging then guides targeted decision making
- NEN therapy choices especially PRRT is driven by Threamostic principles
- PRRT is a complex therapy to deliver and a joint collaborative team approach is strongly advocated
Individualisation of Tumour Therapy: inc Chemo, PBT, MRI Linac, 3T MRI, PET CT

Conventional anti-proliferative chemotherapies

Proliferation

Hypoxia

Receptors/Transporters

Angiogenesis

Hypoxia-directed therapies (EPO, carbogen, HBO, chemotherapy with NLCQ1, TPZ)
Targeting hypoxic fraction (IMRT)

Anti-angiogenic therapy (i.e. Avastin, Cu-chelators)

In summary: it is getting more complex but more exciting!
Thank You
The Era of Molecular Imaging and Therapy