Principles of Theragnostics in Neuroendocrine Tumors: diagnosis and therapy with labelled peptides.

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Direttore Medicina Nucleare IRST-IRCCS, Meldola.
Radiopeptide Therapy: Rationale and Basis for Radioligand Binding

Adapted from: Gray JA, Roth BL. Science. 2002;297(5581):529-531.


Image courtesy of IRST-IRCCS, 100.26, pat. n°60.
**177Lu-DOTATATE therapy schedule**

**Clinical e morphological evaluation**

- Therapy
- + AA
- + AA
- + AA
- + AA

**Follow-up**

- Clinical e morphological evaluation

**MCA (22.2-29.6 GBq)**

* Arginine 12.5 g in 500 ml saline before therapy
* Arginine 12.5 g in 500 ml saline after therapy
* Arginine 12.5 g in 500 ml saline b.i.d. up to two days after therapy
$^{90}$Y-DOTATOC
([90Y-DOTA0-Tyr3]-octreotide)3

<table>
<thead>
<tr>
<th>Affinity (IC50, nM)</th>
<th>sst$_1$</th>
<th>sst$_2$</th>
<th>sst$_3$</th>
<th>sst$_4$</th>
<th>sst$_5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10000</td>
<td>11 ± 1.7</td>
<td>389 ± 13</td>
<td>&gt;10000</td>
<td>114 ± 29</td>
<td></td>
</tr>
</tbody>
</table>

177Lu-DOTATATE
([177Lu-DOTA0-Tyr3]-octreotate)

\[
\begin{align*}
&\text{HOOC} &\text{O} &\text{HOOC} \\
&\text{N} &\text{Cys} &\text{N} \\
&\text{N} &\text{Tyr} &\text{Cys} \\
&\text{N} &\text{D-Trp} &\text{Thr} \\
&\text{N} &\text{Cys} &\text{Lys} \\
&\text{HOOC} &\text{COOH} &\text{Thr (OH)}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Affinity (IC50, nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{sst}_1)</td>
</tr>
<tr>
<td>&gt;10000</td>
</tr>
</tbody>
</table>

PRRT: The IEO-IRST Experience

- **90Y-DOTATOC:**
  - Dosimetry (111In modelling)
  - Phase I studies
  - Efficacy

- **177Lu-DOTATATE:**
  - Dosimetry
  - Phase I-II study

- **Safety and efficacy**
  - Phase II study of 177Lu-DOTATATE in GEP NETs
  - FDG-PET in GEP NETs
  - Randomized trials

IEO/IRST, European Institute of Oncology/Istituto Scientifico per lo Studio e la Cura dei Tumori GEP NET, gastroenteropancreatic neuroendocrine tumor
Internal Dosimetry

- Internal dosimetry deals with the determination of the amount and the spatial and temporal distribution of radiation energy deposited in tissue by radionuclides within the body.

\[ D = \frac{d\bar{E}}{dm} \]

\[ d\bar{E} = \text{Mean energy imparted by ionizing radiation to matter} \]

\[ dm = \text{Mass to which energy is imparted} \]

Objective Response After 4 Cycles of PRRT
$^{90}$Y-DOTATOC: biodistribution and dosimetry

$^{111}$In-DOTATOC: plasma clearance

$^{90}$Y-DOTATOC absorbed dose (Gy/GBq)

- Spleen: 7.2 Gy GBq
- Kidney: 3.8 Gy GBq
- Liver: 0.7 Gy GBq
- M.O.: 0.04 Gy GBq
- Bladder: 2.6 Gy GBq
- Tumor: 1 Gy GBq

**177Lu-DOTATATE**: biodistribution and dosimetry

**Blood clearance**

**Median absorbed doses**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Gy/GBq</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys</td>
<td>0.62</td>
<td>(0.5 - 1.7)</td>
</tr>
<tr>
<td>Liver</td>
<td>0.18</td>
<td>(0.1 - 0.3)</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>0.04</td>
<td>(0.0 - 0.1)</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.64</td>
<td>(0.3 - 2.9)</td>
</tr>
<tr>
<td>Testes</td>
<td>0.16</td>
<td>(0.1 - 0.2)</td>
</tr>
<tr>
<td>U. Bladder</td>
<td>0.31</td>
<td>(0.2 - 0.4)</td>
</tr>
<tr>
<td>Other organs</td>
<td>0.04</td>
<td>(0.0 - 0.1)</td>
</tr>
</tbody>
</table>

Tumours (0.6 – 56) Gy/GBq
Different median creatinine clearance course in risk (red line, tendency continuous line) and no risk (blue line, tendency dotted line) patients treated with $^{90}$Y-DOTATOC over 4 years of follow-up ($R^2=0.9598$)

Comparison of $^{177}\text{Lu}$-DOTATATE vs. $^{90}\text{Y}$-DOTATATE through a retrospective study

Which is more appropriate?
Possible combinations?
Timing? (which first; $\Delta t$)

dosimetry
$^{90}\text{Y}$ versus $^{177}\text{Lu}$

$^{90}\text{Y}$

- **Half-Life**: 64 h (2.6 d)
- **Emission**: pure $\beta^-$ emitter
- $E_{\beta\text{max}} = 2.27$ MeV
- **Range**: 11 mm
- **Chemical form**: C.F. $^{90}\text{YCl}_3$

$^{177}\text{Lu}$

- **Half-Life**: 6.64 d
- **Emission**: $\beta^-$, $\gamma$ emitter
- $E_{\beta\text{max}} = 0.5$ MeV
- **Range**: 2 mm
- **Chemical form**: $^{177}\text{LuCl}_3$
- **main $\gamma$ emissions**: 160 KeV, 202 KeV
absorbed doses: $^{177}\text{Lu}$ vs. $^{90}\text{Y}$

$^{177}\text{Lu}$-TATE Tumours: (0.6 – 56) Gy/GBq

$^{90}\text{Y}$-TATE: Tumours: (2.2–180) Gy/GBq

NORMAL ORGANS $^{90}\text{Y}$

$^{177}\text{Lu}$ $\sim$ 4

TUMOURS $^{90}\text{Y}$

$^{177}\text{Lu}$ $\sim$ 4.5 ($\varnothing > 2\text{cm}$)

2.1 ($\varnothing < 2\text{cm}$)...

Benefit/risk balance remains to be established for each patient based on the TUMOUR / KIDNEY dose ratio
Patient With Bone Marrow Metastases From a Pancreatic G2 NET Treated With PRRT With 177Lu-DOTATATE (25 GBq)

Basal 68Ga-DOTATOC PET-CT

Final 68Ga-DOTATOC PET-CT

Images courtesy of Paganelli G.
ENETS Consensus Guidelines 2016: Midgut NEN

Therapeutic Algorithm for the Management of (Midgut) NEN With Advanced Locoregional Disease

CS, carcinoid syndrome; G, grade; LM, liver metastasis; NEN, neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; PD, disease progression; SD, stable disease; SSA, somatostatin analogue; SSTR, somatostatin receptor

ENETS Consensus Guidelines 2016: Pancreatic NEN
Therapeutic Algorithm for the Management of Pancreatic NEN With Advanced Locoregional Disease and/or Distant Metastases

CXT, chemotherapy
Phase 3 Trial of $^{177}$Lu-Dotatate for Midgut Neuroendocrine Tumors

“Current guidelines place it as an option after other treatments have failed...However, in the future, in certain situations, PRRT may well be considered earlier in the treatment pathway”
The NETTER Study: Trial Design

229 Patients With Midgut NETs

\[ ^{177}\text{Lu-DOTATATE group, 116 patients} \]

\[ ^{177}\text{Lu-DOTATATE} \]

\[ 7.4 \text{ GBq every 8 weeks} \]

\[ + \]

\[ \text{Octreotide LAR} \]

\[ 30 \text{ mg every 4 weeks} \]

\[ \text{Octreotide LAR} \]

\[ 60 \text{ mg every 4 weeks} \]

\[ \text{Control group, 113 patients} \]

The NETTER Study: Results

PFS

PFS, progression-free survival
The NETTER Study: Results

OS (Interim Analysis)

OS, overall survival
The NETTER Study: Health-Related Quality of Life

Time to QoL deterioration (TTD)

\[ ^{177}\text{Lu-DOTATATE group} \]

- Global health status 28.8 months
- Physical functioning status 25.2 months

\[ \text{Control group} \]

- Global health status 6.1 months
- Physical functioning status 11.5 months

QoL, quality of life
# The NETTER Study: Adverse Events

## Safety Population (Cont’d)

<table>
<thead>
<tr>
<th>Event</th>
<th>^177^Lu-DOTATATE Group (N = 111)</th>
<th>Control Group (N = 110)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Blood disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>28 (25)</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (14)</td>
<td>0</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>20 (18)</td>
<td>10 (9)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11 (10)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (5)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>32 (29)</td>
<td>2 (2)</td>
<td>22 (20)</td>
</tr>
<tr>
<td>Nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>20 (18)</td>
<td>0</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>18 (16)</td>
<td>0</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 (11)</td>
<td>0</td>
<td>6 (5)</td>
</tr>
</tbody>
</table>

Risk Factors for Bone Marrow and Kidney Toxicity
Risk Factors for Bone Marrow and Kidney Toxicity

- Diabetes
- Hypertension
- Previous chemotherapy
- Previous PRRT

Different median creatinine clearance course in risk (red line, tendency continuous line) and no risk (blue line, tendency dotted line) patients treated with 90Y-DOTATOC over 4 years of follow-up (R2=0.9598)

GEP NETs: SSTR2 Positive

Risk factors for kidney and bone marrow toxicity

No Risk factors

Risk Factors

$^{177}$Lu 750 mCi in 5 cycles

$^{177}$Lu 500 mCi in 5 cycles
177 Lu-Dota-octreotate radionuclide therapy of advanced gastrointestinal neuroendocrine tumors: results from a phase II study

Giovanni Paganelli · Maddalena Sansovini · Alice Ambrosetti · Stefano Severi · Manuela Monti · Emanuela Scarpi · Caterina Donati · Annarita Ianniello · Federica Matteucci · Dino Amadori

Similar population of NETTER-1 Trial

Results

25 patients received 25.5 GBq

18 patients received 17.8 GBq

Median PFS in Relation to the FD/RD Group

Median OS of the Entire Population and in Relation to the FD/RD Group

Median follow-up: 38 months (range 11-59)

<table>
<thead>
<tr>
<th></th>
<th>N. patients</th>
<th>N. events (%)</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>43</td>
<td>8 (19)</td>
<td>Nr</td>
</tr>
<tr>
<td>FD</td>
<td>25</td>
<td>4 (16)</td>
<td>Nr</td>
</tr>
<tr>
<td>RD</td>
<td>18</td>
<td>4 (22)</td>
<td>Nr</td>
</tr>
</tbody>
</table>

# Results: pNET G1-G2

<table>
<thead>
<tr>
<th>Patients With Disease Progression</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors</td>
<td>28</td>
</tr>
<tr>
<td>With risk factors</td>
<td>32</td>
</tr>
</tbody>
</table>
Results: pNET G1-G2

REDUCED DOSAGE GROUP

- CR: 22%
- PR: 16%
- SD: 59%
- PD: 3%

FULL DOSAGE GROUP

- CR: 14%
- PR: 32%
- SD: 43%
- PD: 11%

CR, complete response; PR, partial response

## Results: pNET G1-G2

### REDUCED DOSAGE GROUP

- 32 patients had **18.5 GBq** (range 11.1-21.4)
- DCR **78.1%**
- Median PFS **21.7 months** (range 18.1-48.2)
- Median OS **63.8 months** (range 28-NR)

### FULL DOSAGE GROUP

- 28 patients had **25.9 GBq** (range 22.2-29.2)
- DCR **85.7%**
- Median PFS **53.4 months** (range 20.1-68.7)
- Median OS not reached

DCR, disease-control rate; NR, not reached

Renal Toxicity

FD, full dose; RD, reduced dose

Bone Marrow Toxicity

PFS According to FDG PET

FDG positive: Median PFS 21.2 months (95% CI 18.1-28.7)
FDG negative: Median PFS 68.7 months (95% CI 53.4-not reached)

\( P < .0002 \)

Role of FDG-PET
FDG-PET With a Prognostic Purpose in NETs

Predictive Value of $^{18}$F-FDG PET and Somatostatin Receptor Scintigraphy in Patients with Metastatic Endocrine Tumors

Imaging, Diagnosis, Prognosis
$^{18}$F-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival of Patients with Neuroendocrine Tumors
FDG-PET–Negative and PET-CT $^{68}$Ga–Positive scan

Images courtesy of Azienda-Ospedaliero-Universitaria di Bologna.
Warburg Effect

Midgut NET, Ki67<3% FDG PET +

Baseline $^{68}$Ga PET

Baseline FDG PET

$^{177}$LU DOTATATE 1° WB

$^{177}$LU DOTATATE 4° WB

Images courtesy of Paganelli G.
Liver Metastases From Unknown NET (FDG-ve)

Basal MRI

Final MRI

Images courtesy of Paganelli G.
A. Positive $^{68}$Ga-PET (negative FDG) in liver and intestinal sites prePRRT
B. Whole-body scintigraphy after 1$^{st}$ cycle of Lu-PRRT
C. Whole-body scintigraphy after 4$^{th}$ cycle of Lu-PRRT
Cumulative activity administered: 22.2 GBq $^{177}$Lu-DOTATATE

FDG-PET With a Prognostic Purpose in NETs


Long-term follow-up and role of FDG PET in advanced pancreatic neuroendocrine patients treated with $^{177}$Lu-DOTATATE

PFS According to FDG PET

FDG positive: Median PFS 21.2 months (95% CI 18.1-28.7)
FDG negative: Median PFS 68.7 months (95% CI 53.4-not reached)

P<.0002

## Multivariate Analysis Related to PFS and Median OS

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>FDG (positive vs negative)</td>
<td>5.15 (1.42-18.75)</td>
<td>5.08 (0.85-30.42)</td>
</tr>
<tr>
<td></td>
<td>.013</td>
<td>.075</td>
</tr>
<tr>
<td>Tumor burden (score 2 vs 1)</td>
<td>3.03 (0.92-9.99)</td>
<td>4.12 (0.41-40.96)</td>
</tr>
<tr>
<td></td>
<td>.188</td>
<td>.477</td>
</tr>
<tr>
<td>Tumor burden (score 3 vs 1)</td>
<td>2.55 (0.75-8.71)</td>
<td>3.98 (0.38-41.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic lesions (grade 1 vs grade 0)</td>
<td>1.54 (0.30-7.80)</td>
<td>1.76 (0.13-22.92)</td>
</tr>
<tr>
<td></td>
<td>.871</td>
<td>.910</td>
</tr>
<tr>
<td>Hepatic lesions (grade 2 vs grade 0)</td>
<td>1.31 (0.31-5.49)</td>
<td>1.54 (0.15-15.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative activity (RA vs FA)</td>
<td>0.85 (0.41-1.76)</td>
<td>2.32 (0.75-7.16)</td>
</tr>
<tr>
<td></td>
<td>.658</td>
<td>.144</td>
</tr>
<tr>
<td>After backward stepwise procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDG (positive vs negative)</td>
<td>4.27 (1.88-9.69)</td>
<td>4.89 (1.35-17.65)</td>
</tr>
<tr>
<td></td>
<td>.0005</td>
<td>.015</td>
</tr>
<tr>
<td>Cumulative activity (RA vs FA)</td>
<td>1.18 (0.60-2.34)</td>
<td>3.17 (1.08-9.34)</td>
</tr>
<tr>
<td></td>
<td>.627</td>
<td>.0361</td>
</tr>
</tbody>
</table>

FA, full activity; mOS, median overall survival; RA, reduced activity

"The presence of increased glycolytic activity of 18FDG tends to increase with tumor grade and has been shown to predict poor survival in NEN ... It may be a more powerful prognostic marker than conventional measures including the percentage of cells staining for Ki-67... "

"Studies combining PRRT with radiosensitizing chemotherapy ... Peptide Receptor Chemoradionuclide Therapy (PRCRT), have shown that is feasible with minimal incremental toxicity ... The rationale ... in strongest for higher grade NEN"

and FDG +ve (Paganelli )

GRADING PROPOSAL FOR NET

GRADE  
(KI 67 index %)  
PET FDG NEGATIVE  
PET FDG POSITIVE

1 (<3)  G1 −ve  G1 +ve
2 (3-20)  G2 −ve  G2 +ve
3a (21-35)  G3a −ve  G3a +ve
3b (>35)  G3b −ve  G3b +ve
Randomized Studies at IRST

- The LU-P-PET randomized trial
GEP NETs SSTR2-Positive G1-G2, G3 (<35%)  

FDG PET

NEGATIVE: LU-NET  

POSITIVE: LU-CAS

$^{177}$Lu 700 mCi  vs  $^{177}$Lu 500 mCi  

$^{177}$Lu  750 mCi + Cap vs  750 mCi $^{177}$LuDotatate
Take Home Messages

• Stop “one fits all” concept in PRRT!
• More intensive therapy protocols in FDG PET+ ve cases
• Randomized trials needed