Dosimetry for Radiopeptide therapy

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Peptide Receptor Radionuclide Therapy
PRRT

- Therapy for tumours with Somatostatin Sub-type 2 receptors
  - Theranostics: $^{68}\text{Ga}}$-DOTA-octreotate/tide PET scan

- Started out with $^{111}\text{In}}$-DTPA-octreotide
- Phase I / II studies $^{90}\text{Y}}$-DOTA-octreotide
  - Dosimetry with $^{86}\text{Y}}$-DOTA-octreotide

- Phase II / III studies with $^{177}\text{Lu}}$-DOTA-octreotate
  - Peri-therapy dosimetry using $^{177}\text{Lu}}$-DOTA-octreotate
**90Y-DOTA-octreotide renal dosimetry**

Dosimetry is possible with 

- $^{86}$Y (14.7 h $T_{1/2}$ $\beta^+$ emitter)
- $^{90}$Y (64.1 h $T_{1/2}$ $\beta^-$ emitter)

- Infusion of amino-acids
  46% reduction in absorbed dose kidneys

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Personalized kidney dosimetry for $^{90}$Y-DOTA-octreotide

A. MIRD phantom kidney (150g)
B. CT-based volume (120-250 ml)
C. Change from dose to BED

Biologically Effective Dose

$$BED = D \times "Relative Efficiency"$$

Correction for dose rate

$$MTA = 3 \times 4.44 \text{ GBq} = 13.32 \text{ GBq}$$

Correlation between KAD or BED, and the loss in CLR. (A)

Dose-effect relation for late occurring kidney toxicity after $^{90}$Y-DOTATOC therapy  

MIRD pamphlet 20, 2008

\[ \text{BED} = D \left( 1 + \frac{T_{\text{repair}}}{T_{\text{eff}} + T_{\text{repair}}} \right) \times \frac{D}{N} \times \frac{\beta}{\alpha} \]

- Effective half-life: \( T_{\text{eff}} = \frac{T_p T_{\text{clr}}}{T_p + T_{\text{clr}}} \)

\[ LQ \text{ model} \]

\[ \alpha / \beta = 2.5 \text{ Gy}, \]

\[ T_{\text{rep}} = 2.8 \text{ h} \]
Phase II study $^{90}$Y-DOTA-octreotate

- Chemotherapy-like approach
  - MTA 13.32 GBq $2 \times 3.7$ GBq/m$^2$
  - 4 h Amino-Acid infusion
  - No dosimetry

- 102 patients (9%) experienced severe permanent renal toxicity
  - 67 patients grade 4 (dialysis)
  - 35 patients grade 5 (death)

A Imhof et al., J. Clin Onc 2011; 29:2416-2423
Dosimetry for $^{177}$Lu-DOTA-tyr$^3$-octreotate

- Dosimetry assessments
  - Kidneys
  - Tumour lesions
  - Bone marrow (maybe)

$T = 0 \quad T = 1 \text{ day} \quad T = 4 \text{ days} \quad T = 7 \text{ days}$
Nephrotoxicity observed at Erasmus MC after 4 x 7.4 GBq $^{177}$Lu-DOTA-Octreotate


**Erasmus MC**
- 323 patients
- 228 dose < 23 Gy
- 191 ≥ 1 y f.u.
Dose distribution in the kidneys on smaller scale

Ex-vivo autoradiography kidney-uptake
\(^{111}\text{In-DTPA-octreotide}\)

Different dose distributions

M.Melis et al., J Nucl Med 2010

M.Konijnenberg et al., J Nucl Med 2007
Dose model for $\alpha$-emitters on functional subunit scale

Dosimetry for $\alpha$-particle emitters $^{225}\text{Ac} / ^{213}\text{Bi}$

Range $\alpha$-particles:
- 5.9 MeV $^{225}\text{Ac}$: 47 $\mu$m
- 8.4 MeV $^{213}\text{Bi}$: 85 $\mu$m

Size human nephron:
- Glomerulus 150 $\mu$m
- Tubule lumen 33 $\mu$m

Figure 1. Idealized geometrical nephron model. The parameters shown are those used for the simulation: $r_1$ is the proximal tubule radius, $r_l$ is the lumen radius as measured by histology. The $\varepsilon$ value is taken to be 1 $\mu$m and corresponds to interstitial space, $h_1$ and $h_2$ represent the scale of the proximal tubule length.
Bone marrow toxicity (11% > grade 3)

Subacute haematotoxicity after PRRT with $^{177}$Lu-DOTA-octreotate: prognostic factors, incidence and course


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Platelet count

White blood cells

Fig. 2 Venn diagram of haematological toxicity (grade 3/4) in 34 out of 320 patients treated with a median cumulative dose of 29.6 GBq $^{177}$Lu-DOTATATE
Persistent Hematologic Dysfunction after Peptide Receptor Radionuclide Therapy with $^{177}$Lu-DOTATATE: Incidence, Course, and Predicting Factors in Patients with Gastroenteropancreatic Neuroendocrine Tumors

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**FIGURE 3.** Expected number of patients with hematopoietic neoplasms and type, based on data from The Netherlands Cancer Registry, as well as observed number of patients (of 274 GEP NET patients) with PHD after PRRT with $^{177}$Lu-DOTATATE, including 8 patients with hematopoietic neoplasms and 3 with BM failure. Red = MDS; orange = AML; yellow = MPN + MDS/MPN; green = BM failure.

**FIGURE 5.** Comparison of PHD and cumulative dose to BM. (A) Cumulative estimated BM dose in 11 patients with PHD (including 5 AML/MDS), and 6 other diagnosis patients and 263 patients without PHD. (B) Marrow dose in 3 patients with AML/MDS and 28 patients without AML/MDS. Data for dosimetry analysis in subgroup of 807 patients were adopted from Bodei et al. Whiskers represent minimum and maximum estimated BM dose in grays. Height of box shows interquartile range, and horizontal line in box is median estimated BM dose in grays.
Dose Response of Pancreatic Neuroendocrine Tumors Treated with Peptide Receptor Radionuclide Therapy Using $^{177}$Lu-DOTATATE

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FIGURE 3. Tumor dose–response relationship in 13 patients treated with $^{90}$Y-DOTATOC. Tumor volumes were assessed by CT before and after treatment. Tumor dose estimates were derived from CT scan volume measurements and quantitative $^{90}$Y-DOTATOC imaging performed before treatment. Data were further computed using the MIRDose Spheric model.

FIGURE 5. Tumor dose–response relationship for patients with PNETs treated with PRRT using $^{177}$Lu-DOTATATE, including tumors larger than 2.2 cm (A) and only tumors larger than 4 cm (B). Solid lines represent 2-parameter sigmoid fits ($y = 100/(1 + (x/\beta)^\alpha)$), where $\alpha$ and $\beta$ are fitting parameters. Parameters $\alpha$ and $\beta$ were 445 and 0.79, with SEs of 104 and 0.14, respectively, for tumors larger than 2.2 cm and 504 and 0.84, with SEs of 83 and 0.1, respectively, for tumors larger than 4 cm. Pearson correlation coefficients ($R^2$) were 0.62 (A) and 0.91 (B).

Practical Dosimetry of Peptide Receptor Radionuclide Therapy with $^{90}$Y-Labeled Somatostatin Analogs


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Tumour doses > 150 ~ 200 Gy
Variation in absorbed dose values at 4 x 7.4 GBq

- Absorbed dose
- Kidneys:
  - 4 x (6 ± 2) Gy
- Bone marrow:
  - 4 x (0.5 ± 0.1) Gy
- Tumour
  - 4 x 50 (10 - 120) Gy

M. Cremonesi et al. EJNMMI 2018
Prospective clinical trial (N x 7.4 GBq) to treat to the maximum tolerated dose

- Proceed with 7.4 GBq $^{177}$Lu cycles
- Until the kidneys BED = 40 Gy

**ILUMINET—trial design**

**Step 1**
- $^{177}$Lu 7.4 GBq
- $^{177}$Lu 7.4 GBq
- $^{177}$Lu 7.4 GBq

**Step 2**
- $^{177}$Lu 7.4 GBq
- $^{177}$Lu 7.4 GBq

**BED:**
- 27 ± 2 Gy

**GO if:**
- Kidneys ok
- Bone marrow ok
- No PD
- No toxicities

**STOP**
- Age
- Previous therapy
- Adverse event
- Still PD

**Patient population**
- mNET
- G1-2
- PD

Sundlöv et al. EJNMMI Physics (2018) 5:12
Illuminet trial dosimetry:
2D Planar and 3D SPECT absorbed dose assessments

WB at 1 h
WB at 24 h

SPECT at 24 h
Dosimetry guided therapy:

- 23 Gy to the kidneys
  - \( \leq 4 \times 7.4 \text{ GBq } ^{177}\text{Lu} \text{ DOTAtate} \) in 102 patients
  - 5-9 \( \times 7.4 \text{ GBq } ^{177}\text{Lu} \) (N=98)

- Overall median survival
  - 54 months (reached 23 Gy)
  - 25 months (< 23 Gy)
Salvage therapy (repeat 7.4 GBq):

- 4 × 7.4 GBq $^{177}$Lu DOTATate
- 2 × 7.4 GBq $^{177}$Lu (N=168)
- 2 × 7.4 GBq $^{177}$Lu (N=13)
- Cumulative 26-61 GBq

Overall median survival

- GEPNET: 81 m vs. 51 m (control)
- Midgut NET: 77 m vs. 51 m (control)
- Pancreas NET: Not significant
Comparisons in overall survival
(don’t tell the statistician)

Netter-1 study (N=229) in Midgut Neuroendocrine Tumours
(J. Strosberg et al., NEJM 2017)

• > 30 months vs 20 months (control)
The maximum benefit from dosimetry guidance in PRRT with $^{177}$Lu?

- Select the non-responders to fixed dosing schemes 4 x 7.4 GBq:
  - Pancreatic NET
  - Non-responders according to PPQ genetic NET test (L. Bodei et al. EJNMMI (2018) 45:1155–1169)
- Wait for the overwhelming results from the Illuminet trials
Conclusion radiopeptide dosimetry

- Dosimetry save lives in $^{90}$Y-DOTA-octreotide therapy
  - Number of therapy cycles matter
  - Dose-effect relation for renal toxicity using BED
- Bone marrow absorbed dose does not correlate with toxicity
- Prospective trial based on MTD (40 Gy BED)
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