Dosimetry in Nuclear Medicine Therapies

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## Therapies

- Radioiodine
- Phosphonates
- Metabolites (e.g. $^{131}$I-mIBG)
- Radiopeptides
- Radioimmunotherapy
- Radiosynoviothesis
- Intracavitary Therapy
Background

- In comparison to conventional pharmaceuticals, radiopharmaceuticals suite for relatively simple quantification
- The first treatment with radioiodine was described in 1942
- In radioiodine therapy pretherapeutic dosimetry is demanded by law
- Most often the “Marinelli Formula” is used
- This formula was first described 1948\(^1\)

### Marinelli Formula

Used in radioiodine therapy for benign thyroid disorder

\[
\text{Activity} = K \times \frac{\text{Absorbed Dose} \times \text{Volume}}{\text{Max. Uptake} \times \text{eff. Half-life}}
\]
## Radiopeptides

- Many new peptides are in preclinical studies.
- The options for diagnostic and therapy with radiopeptides will increase.
- In therapy the dose limiting toxicity is usually severe and has to be avoided.
- Therefore, a safe but effective activity has to be defined.
- Individual pretherapeutic dosimetry is desirable.
DOTATOC

- Somatostatin analogue
- A high density of somatostatin receptors is found on many tumors, mainly neuroendocrine tumors
- Therapies with Y-90 labelled DOTATOC were started in Basel in 1996
- More than 700 patients are treated so far
Magic Bullet Approach

Application  Distribution  Accumulation

Tumor

Metastases
DOTATOC

DOTA — D-Phe — Cys — Tyr — D-Trp — Lys

In, Ga, Y, Lu

Thr(ol) — Cys — Thr

Institut für Medizinische Bildgebung
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Nuclear Medicine
<table>
<thead>
<tr>
<th>Disease State</th>
<th>Count</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Partial remission</td>
<td>26</td>
<td>89%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>13</td>
<td>11%</td>
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</tbody>
</table>
20h p.i.; 7400 MBq $^{90}$Y-DOTATOC
Neuroendocrine tumor of the pancreas

Metastases

Kidneys!
20h p.i.; 7400 MBq $^{90}$Y-DOTATOC

Neuroendocrine tumour of the pancreas

Correlating CT-scan
SPECT / CT mit $^{111}$In-Octreotid
\(^{68}\text{Ga}-\text{DOTATOC-PET}\)

- Highly specific for visualisation of somatostatin receptor positive tumor tissue
- Anatomic localisation is difficult in certain cases

\rightarrow \text{PET-CT}
$^{68}$Ga-DOTATOC-PET
A Comparison of $^{111}$In-DOTATOC and $^{111}$In-DOTATATE: Biodistribution and Dosimetry in the Identical Patients with Metastatic Neuroendocrine Tumors

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Background

• Both, $^{177}\text{Lu}$-DOTATATE (DOTA-Tyr$^3$-Thr$^8$-Octreotide) and $^{90}\text{Y}$-DOTATOC (DOTA-Tyr$^3$-Octreotide), are used for Peptide Receptor Mediated Radionuclide Therapy (PRMRT) in patients with metastatic neuroendocrine tumours.

• No direct comparison of biodistribution and dosimetry in patients has been performed with those two compounds.
DOTA-TOC
DOTA-Tyr$^3$-Octreotide

DOTA-TATE
DOTA-Tyr$^3$-Thr$^8$-Octreotide
Methods

- 5 male patients (50-74 years) with known metastatic neuroendocrine tumours.

- All Patients were pretreated with $^{90}$Y-DOTATOC. Time since treatment 14 - 25 months.
Methods

• Injection of 222 MBq $^{111}$In-DOTATOC and 222 MBq $^{111}$In-DOTATATE respectively in an interval of 2 weeks.

• Whole body scans were performed immediately, 1, 2, 4, 24 and 48 hours after injection with a dual head camera.

• Blood samples were drawn 10, 20, 30 and 60 minutes and 2, 4, 24 and 48 hours after injection.

• Urine was collected up to 48h p.i. (0-2 h, 2-4 h, 4-24 h, 24-48 h).
Methods

- We used $^{111}$In as a surrogate for $^{90}$Y.
- The dose for the whole body, the liver, the spleen, the kidneys and the clearly visible tumours were calculated with ROI-Technique and MIRDOSE 3.0.
- The dose to the red marrow was calculated from the activity in the blood.
- We used a compartment-model a described by Cremonesi et al. (EJNM, August 1999).
Bloodclearance

%IA

DOTATOC

DOTATATE

time [h]
Absorbed Doses

- DOTATOC
- DOTATATE

Kidneys: p = 0.135
Liver: p = 0.031
Spleen: p = 0.205
Red Marrow: p = 0.591
Tumour-to-Kidney-Ratio

DOTATOC
DOTATATE

Patient 1
Patient 2
Patient 5
Patient 4
222 MBq $^{111}$In- DOTATOC 24h p.i. 222 MBq $^{111}$In- DOTATATE
## Comparison of Absorbed Doses

<table>
<thead>
<tr>
<th>derived from</th>
<th>Forrer et al. $^{111}$In-DOTATOC</th>
<th>Cremonesi et al. $^{111}$In-DOTATOC</th>
<th>Förster et al. $^{86}$Y-DOTATOC</th>
<th>Krenning et al. $^{86}$Y-DOTATOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>2.84 (±0.64)</td>
<td>3.31 (±2.22)</td>
<td>2.73 (±1.41)</td>
<td>2.1 (±0.78)</td>
</tr>
<tr>
<td>Liver</td>
<td>0.92 (±0.35)</td>
<td>0.72 (±0.57)</td>
<td>0.66 (±0.15)</td>
<td>-</td>
</tr>
<tr>
<td>Spleen</td>
<td>6.57 (±5.25)</td>
<td>7.62 (±6.30)</td>
<td>2.32 (±1.97)</td>
<td>1.83 (±1.45)</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.17 (±0.02)</td>
<td>0.03 (±0.01)</td>
<td>0.049 (±0.002)</td>
<td>0.11 (±0.06)</td>
</tr>
</tbody>
</table>
Variability in receptor homogeneity
Radioimmunotherapy

- Radioimmunotherapy (RIT) showed convincing results with $^{90}$Y and $^{131}$I labelled antibodies in treatment of B-cell lymphoma
- The monoclonal antibody Rituximab is widely used for treatment of malignant lymphoma
- We are performing a clinical phase I/II study with $^{177}$Lu-DOTA-Rituximab
Radioimmunotherapy with Lutetium-177-DOTA-Rituximab
A Phase I/II - Study in Patients with Follicular and Mantle Cell Lymphoma

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Chimeric Radiolabelled Antibody

\[ F_v = \text{variable fragment} \]
\[ F_c = \text{constant fragment} \]

binding site

Chelator (DOTA)

Radionuclide (\( ^{177}\text{Lu} \))

murine part

human part
Protocol $^{177}$Lu-DOTA-Rituximab

- Staging: $[^{18}F]$ FDG-PET, CT, bone marrow biopsy, blood counts, chemistry incl. creatinine
Protocol $^{177}$Lu-DOTA-Rituximab

- Scintigraphic images, blood and urine samples up to 15 days p.i.
- Weekly blood counts and chemistry to week 8 or after resolution of nadir, then monthly
- Restaging after 2 month
Blood Clearance

![Diagram of blood clearance over time]

- % IA vs. Time p.i. [h]

Universitätsspital Basel

Nuclear Medicine
2035 MBq (55 mCi) $^{177}$Lu-DOTA-Rituximab
FDG-PET  $^{177}$Lu-DOTA-Rituximab  FDG-PET

Pre  4d p.i.  Post
State of the art dosimetry in Nuclear Medicine

- In treatment of benign thyroid disorders obligatory
- Malignant thyroid tumors: fixed doses
- Phosphonates: fixed dose
- Radiopeptide: most often adapted to body surface
- Radioimmunotherapy: adapted to body weight / body surface
Conclusions

• Dosimetry in Nuclear Medicine therapy is not well established

• Accurate dosimetry could probably decrease toxicity

• New methods like SPECT-CT and PET-CT will help to simplify dosimetry

• In routine treatments a simple, accurate way of dosimetry is needed!
Conclusions

• To define a maximum tolerated injected activity, the maximum tolerated dose of normal tissue has to be known

• Not enough data are existing for low-dose-rate radiation

• Inhomogeneous distribution of activity causes problems in dosimetry
Thanks for your attention