Quantitative Theranostics in Nuclear Medicine

M. Lassmann
Contents

- What is Theranostics?
- Potential Targets
- Basic Principles of Quantitative Theranostics
  - Isotopes
  - Imaging
  - Dosimetry
- Clinical Applications
  - Diagnostics and Treatment of Differentiated Thyroid Cancer
  - Diagnostics and Treatment of Neuroendocrine Tumors
- Conclusion and Outlook
Origin of Theranostics

Definition
The term “theranostics” was probably first used in 2000 to describe the business model of developing diagnostic tests directly linked to the application of specific therapies.
Theranostic – number of PubMed entries
Concept and Aim

Combination of predictive biomarkers with an effective therapeutic agent

Selection of patients who are most likely responding or most likely not responding from this specific treatment; “personalized medicine”
Metabolic active radiopharmaceuticals

- Radioiodine therapy of benign and malignant thyroid diseases

Specifically binding radiopharmaceuticals

- Peptide-receptor radionuclide therapy (PRRT) of neuroendocrine tumors
- Prostate-specific membrane antigen (PSMA) therapy of prostate cancer
- (Chemokine receptor 4 (CXCR4) therapy)

More to come …..
First Application of Theranostics

What is Theranostics?
Potential Targets
Basic Principles
Clinical Applications
Outlook and Challenges

RADIOACTIVE IODINE THERAPY
Effect on Functioning Metastases of Adenocarcinoma of the Thyroid
S. M. SEIDLIN, M.D.; L. D. MARINELLI, M.A.; ELEANOR OSHRY, B.S.

Neuroendocrine Tumors

What is Theranostics?

Basic Principles

Clinical Applications

Outlook and Challenges

68\text{Ga}-\text{DOTATATE}-\text{PET}

177\text{Lu}-\text{DOTATATE} 1^{\text{st}} \text{ cycle}

68\text{Ga}-\text{DOTATATE}-\text{PET}

Partial response
PSMA - Theranostics

73y M with metastatic prostate cancer (bone, LN)

$^{68}$Ga-PSMA PET/CT  Pretherapeutic $^{177}$Lu-PSMA  Posttherapeutic $^{177}$Lu-PSMA
CXCR4 – Theranostics

[\textsuperscript{68}Ga]Pentixafor

Before [\textsuperscript{177}Lu]Pentixather

24 hours p.i.

15 days p.i.

[\textsuperscript{177}Lu]Pentixather

Herrmann et al, J Nucl Med 2016
## Transitioning into Clinical Reality - Overview

<table>
<thead>
<tr>
<th>Target</th>
<th>Disease</th>
<th>Predictive Biomarker</th>
<th>Therapeutic</th>
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</thead>
<tbody>
<tr>
<td>Na/I-symp.</td>
<td>Thyroid Cancer</td>
<td>$^{124}$I, ($^{99m}$Tc)</td>
<td>$^{131}$I</td>
</tr>
<tr>
<td>SSTR2</td>
<td>NETs, SCLC</td>
<td>$^{68}$Ga-Dotatate</td>
<td>$^{177}$Lu-Dotatate</td>
</tr>
<tr>
<td>PSMA</td>
<td>Prostate Cancer</td>
<td>$^{68}$Ga-PSMA</td>
<td>$^{177}$Lu-$^{131}$I-PSMA</td>
</tr>
<tr>
<td>CXCR4</td>
<td>Multiple Myeloma, CLL, SCLC etc.</td>
<td>$^{68}$Ga-Pentixafor</td>
<td>$^{177}$Lu-$^{90}$Y-Pentixather</td>
</tr>
</tbody>
</table>

More to come ……
<table>
<thead>
<tr>
<th>Isotope</th>
<th>Halflife (h)</th>
<th>$\beta_{\text{max}}$ (MeV)</th>
<th>$\gamma$ (keV)</th>
<th>Max. range (mm)</th>
<th>Remarks</th>
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</thead>
<tbody>
<tr>
<td>$^{68}\text{Ga}$</td>
<td>1.13</td>
<td>1.9</td>
<td>-</td>
<td>10</td>
<td>PET</td>
</tr>
<tr>
<td>$^{124}\text{I}$</td>
<td>100</td>
<td>2.1</td>
<td>603</td>
<td>11</td>
<td>positrons + prompt gamma emission</td>
</tr>
<tr>
<td>$^{90}\text{Y}$</td>
<td>64</td>
<td>2.3</td>
<td>-</td>
<td>12</td>
<td>Very low positron branching ratio</td>
</tr>
<tr>
<td>$^{131}\text{I}$</td>
<td>192</td>
<td>0.61</td>
<td>364</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>$^{177}\text{Lu}$</td>
<td>161</td>
<td>0.50</td>
<td>208</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>

More to come ……
Recovery Coefficients for Several PET Isotopes

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SPECT/CT

**integrated CT**

- morphologic correlation
- Measurement of the attenuation map
- Scatter correction by using triple window techniques
- quantitative Analysis
Quantitative SPECT

- Isotope
- Energy Resolution
- Collimator
- Electronics
- Spatial Resolution
- Calibration Source
- Attenuation
- Scatter
- Noise
- Reconstruction
- Partial Volume Effect

MIRD Pamphlets 23, 24, 26

Results of the METROMRT project
Relative deviations as a function of the effective number of iterations for $^{177}$Lu
The administered activity distributes in the body. Based on cellular functions and physiology, it accumulates in individual organs in a different way (biodistribution and biokinetics). Source organs irradiate target organs, self-irradiation of organs is also possible. For assessing radiation-related risks, the absorbed dose in the individual organs needs to be calculated. For calculating absorbed dose, a formalism called MIRD*-Scheme was developed in 1976 (summing over all organ contributions).

* Medical Internal Radiation Dose - committee of the SNMMI
„Simple Dosimetry“

- Measurement of the time-activity curve (TAC)
- Integration of the TAC in order to obtain the total number of decays
- Multiplication with the corresponding dose factors

\[ D(r_T) = \sum_S \left( \int A(r_S, t) dt \cdot S(r_T \leftarrow r_S) \right) \]
Internal dose estimates – “marriage” of physical and biological quantities:

- **Biology** – distribution and kinetics
- **Physics** – energy deposition patterns

\[
D(r_T) = \sum_S \left( \int A(r_S, t) dt \cdot S(r_T \leftarrow r_S) \right) = \tilde{A}_h \cdot S(k \leftarrow h)
\]
Integrating the time-activity curve

Figure 1.—Radioactivity uptake in the kidneys of a patient, injected with $^{111}$In-DTPA-octreotide (left graph) and with $^{86}$Y-DOTA-octreotide (right graph). Three curve fitting methods were used for establishing the time-activity curve: the trapezoid method, a single exponential and by compartmental modelling.

Dosimetry - Mass Adjustment

For SELF Irradiation Only

\[ S_{r \leftarrow r}(\text{patient}) = S_{r \leftarrow r}(\text{standard}) \cdot \frac{\text{Mass}_r(\text{standard})}{\text{Mass}_r(\text{specific})} \]
Patient specific dosimetry

Patient CT

Specific S values

voxel
The Role of Dosimetry in the Treatment of Thyroid Cancer

Lesion Dosimetry (Efficacy)

Blood (Bone Marrow) Dosimetry (Safety)

Dose to the Lesion in Gy/GBq

Critical Blood Activity (max 2 Gy)

L. Freudenberg et al. 2007
Lesion Dosimetry

Gamma camera based dosimetry:

- Uptake measurements not very precise
- Attenuation correction difficult
- No correction for scattering
- Lesion volume difficult to determine

I-124-PET based dosimetry

- Image resolution excellent
- Precise determination of lesion uptake
- Correction for attenuation and scattering
- Lesion volume can be estimated
Tumor dosimetry with $^{124}\text{I}$

Voxel-based Dosimetry with $^{124}\text{I}$, 15 GBq $^{131}\text{I}$, Sgouros et al. JNM 2004

- 100 Gy (5-720)
- 350 Gy (37-1000)
- 170 Gy (17-760)
- 100 Gy (6-880)

What is Theranostics?
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Results – Tumor Doses

Frequency distribution of the mean absorbed dose calculated for 56 different lesions

Voxel-based Dose range: 
< 1 Gy – 4000 Gy
Absorbed Doses to Metastases in a DTC Patient

Post-therapy scintigram

Radioiodine kinetics of the osseous metastases

\[
D(r_T) = \sum_S \left( \int A(r_S, t) dt \cdot S(r_T \leftarrow r_S) \right)
\]
The Role of Dosimetry in the Treatment of Thyroid Cancer

Lesion Dosimetry (Efficacy)

Dose to the Lesion in Gy/GBq

Blood (Bone Marrow) Dosimetry (Safety)

Critical Blood Activity (max 2 Gy)

L. Freudenberg et al. 2007
Absorbed Dose to the Blood in DTC Patients

3.7 GBq I-131

0.38 Gy

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DNA damage foci formation: $\gamma$-H2AX and 53BP1

- The most critical effects of ionizing irradiation are DNA double strand breaks (DSBs)

- Biomarkers for DSBs
  - phosphorylation of the protein “histone H2AX”
    - $\gamma$-H2AX
  - Accumulation of the damage sensor 53BP1 in the vicinity of the DSB

- Immunofluorescence staining
- microscopically visible foci
- co-localization of $\gamma$-H2AX and 53BP1
DNA damage in lymphocytes after radioiodine therapy

- Almost linear function of the dose up to 2 h, followed by a bi-exponential decay. Induction of a fast repair component, maximum at 3.2h
Ga-68-PET correlates with tumor absorbed doses in menigioma

PET SUV correlates with radionuclide uptake in peptide receptor therapy in meningioma

Herrbert Hänschfeld · Reinhard A. Sweeney · Michael Flett · Andreas K. Buck · Mario Lühr · Samuel Samnich · Michael Kreissl · Frederik A. Verburg
Experimental facts supporting a red marrow uptake due to radiometal transchelation in $^{90}$Y-DOTATOC therapy and relationship to the decrease of platelet counts

Stephan Walrand · Raffaella Barone · Stanislas Pauwels · François Jamar

Prediction using Y-86:
Closed triangles: Radiation accidents (WB irradiation)
Continuous Line: Fit
Kidney toxicity in PRRT (Y-90)

Dose response curve for the correlation of the BED to the kidney with symptomatic radiation damage to the kidneys for both the external beam data as compared to the $^{90}$Y-DOTA-octreotide data.

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**MIRD Pamphlet No. 20: The Effect of Model Assumptions on Kidney Dosimetry and Response—Implications for Radionuclide Therapy**

Universitätsklinikum Würzburg
Dosimetry in PRRT with $^{177}$Lu

**Individualized Dosimetry of Kidney and Bone Marrow in Patients Undergoing $^{177}$Lu-DOTA-Octreotate Treatment**

Mattias Sandström$^{1,2}$, Ulrike Garske-Román$^{2,3}$, Dan Granberg$^3$, Silvia Johansson$^2$, Charles Widström$^1$, Barbro Eriksson$^3$, Anders Sundin$^{2,4}$, Hans Lundqvist$^5$, and Mark Lubberink$^2$

The concept of using short-lived tracers for diagnostics and long-lived tracers for therapy, both coupled to the same molecule, becomes increasingly important.

In most cases, $^{68}$Ga labelled diagnostic compounds are not suited to predict therapy absorbed doses due to its short half-life (unlike $^{124}$I). They can, however, be used for determining the success of a therapy.

Dosimetry in molecular targeted therapies still lacks accuracy because of inherent methodological issues with:
- Quantitative Imaging
- Integration of the Time-Activity Curve
- Determination of the S-Values

New biomarkers link physical dosimetry to biological effects.

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Theranostics - What do we NOT know?

- $^{124}$I: When will it become available on a large scale?
- Is a semi-quantitative interpretation of a $^{68}$Ga scan good enough for predicting the success of a therapy?
- Does $^{68}$Ga imaging just provide confirmation visibility of lesions or can it also predict toxicity?
- What is the role of dosimetry in $^{177}$Lu based treatment? Will it be required for every patient?
- What are the toxicity limits for $^{177}$Lu-based treatments?
- Other Isotopes / Compounds?