FMU-ICRP Workshop on Radiological Protection in Medicine
“Current Status in Radionuclide Therapy”
Tuesday, October 3, 2017
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Kindai University Faculty of Medicine, Osaka, Japan
Current Status in Radionuclide Therapy

- Prologue
- Conventional RNT
- Radium-223 dichloride
- Theranostic approach
  - Somatostatin Receptor Radionuclide Therapy
  - Prostate-specific membrane antigen (PSMA ligands)
  - Hematology
  - Hypoxia (Cu-64 ATSM)
- Targeted Alpha-Particle Immunotherapy
- Pretargeting: how to enhance tumor-to-normal
Kawamata town, Fukushima

Population: 15,352 (as of May 1, 2011)
Industry: Silk Products, Chicken, IT Products

Collaboration with Kindai University for Reconstruction from Disaster and Protection of Children
Kawamata town

Kawamata town, Fukushima Pref.

Planned Evacuation Zone (20mSv/year)

Evacuation in case of emergency

Evacuation Zone (20km)
$^{131}$I Therapy for Thyroid Cancer

Pre

Post
131I Therapy in Shanghai Hospitals
Radium-223 Dichloride for Treatment of Bone Metastases

Radium is alkaline earth as Calcium.
Alpha-particles have a much shorter range of action than beta-particles (such as strontium-89 and samarium-153), permitting more selective cancer cell killing and less bone marrow toxicity.
The high linear-energy transfer (LET) radiation produced by alpha-particles induces double-strand DNA breaks in adjacent tumor cells and is more effective at killing cancer cells than the low-LET radiation produced by beta-particles.
ALSYMPCA
Overall Survival in Patients with CRPC and Symptomatic Bone Metastases

In an updated analysis of ALSYMPCA, radium-223 significantly improved OS by 3.6 months versus placebo.

P value is for descriptive purpose only.

Parker C et al. ESMO 2013 Abstr. 2.878
In ALSYMPCA, radium-223 significantly improved time to first symptomatic skeletal event (SSE) versus placebo.

SSEs included only clinically relevant pathologic bone fractures, not asymptomatic compression fractures.

P value is for descriptive purpose only.

Parker C et al. ESMO 2013 Abstr. 2.878
Theranostic approach

Imaging, RNT, and Imaging

Imaging
Staging
Planning

RNT

Imaging
Response
Dosimetry

PET/CT

SPECT or SPECT/CT
Whole-body anterior images for patient 3 acquired at 4 (A), 24 (B), 48 (C), 72 (D), and 144 h (E) after administration. Sarah J. Chittenden et al. J Nucl Med 2015;56:1304-1309
Now: Standard 55kBq/kg x 6 injections (every 4 weeks)
Future: Individualized protocol based on dosimetry

Absorbed dose (in mGy/MBq) for bone surfaces (A), red marrow from blood (B), kidneys (C), bladder wall (D), liver (E), and whole body (F). Sarah J. Chittenden et al. J Nucl Med 2015;56:1304-1309
Somatostatin Analogs for Treatment of Neuroendocrine Tumors

**DOTA-OC**

**DOTA-TOC**

**DOTA-TATE**

P. Powell and H.R. Mäcke

$^{111}$In-DTPA-octreotide: FDA approval in 1994

- Imaging: $^{99m}$Tc, $^{111}$In, $^{68}$Ga etc.
- Therapy: $^{177}$Lu, $^{90}$Y, $^{213}$Bi etc.
2 x $^{90}$Y-DOTATOC in NETs (Theranostic approach)
Large open label phase II study, N = 1109

Overall Survival

- Median OS 36 months
- Median OS 22.8 months
- Median OS 20.4 months

NETTER-1 study

**TREATMENT AND ASSESSMENTS**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lutathera + Sandostatin LAR 30 mg</td>
</tr>
<tr>
<td>2</td>
<td>4 administrations of 7.4 GBq Lutathera every 8 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Sandostatin LAR Arm</td>
</tr>
<tr>
<td>4</td>
<td>60 mg Octreotide LAR treatment every 4 weeks</td>
</tr>
</tbody>
</table>

**PROGRESSION FREE SURVIVAL BY RECIST EVERY 12 WEEKS**

**Baseline and Randomization**

- n = 115

**Follow-up**

- 5 yr Follow-up
N = 229 (ITT)
Number of events: 90

- $^{177}$Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio: **0.21** [0.129 – 0.338] \( p < 0.0001 \)

**79% reduction** in the risk of disease progression/death

Estimated Median PFS in the $^{177}$Lu-Dotatate arm ≈ 40 months

Progression-Free Survival

All progressions centrally confirmed and independently reviewed for eligibility (SAP)
Prostate cancer

- Antitumour activity of $^{177}$Lu-PSMA617 in metastatic hormone-refractory prostate cancer by Kratochwil and coworkers from the University of Heidelberg.

- A total of 30 patients have undergone three treatment cycles in intervals of 2 months each. After a third treatment cycle, reduction in PSA levels was >50 % in more than 70 % of patients, indicating highly effective tumour cell kill.

EANM2015
PSMA Ligands

**Figure 2**: Small-molecule PSMA ligands currently being investigated for PCA imaging in clinical settings. All possess the characteristic glu-urea-lys core.

Lütje et al. Theranostic 2015:5:12
Multiple Myeloma

$^{177}$Lu- or $^{90}$Y-labelled CXCR4-specific ligands (Pentixather®)

- > 50% decrease in ratio involved/uninvolved serum FLC as response to Pentixather

- PET/CT: PR (ΔSUVmax >35%, #1) and CR (#3)
- OS: 6 months (#1) and 3 months (#3)

EANM2015
Cu-64 ATSM
Cu-diacetyl-bis(N 4-methylthiosemicarbazone)
Hypoxia Targeting
β+ particles: PET imaging & Therapy

Targeted Alpha-Particle Immunotherapy for Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Particle(s) Emitted</th>
<th>Half-Life</th>
<th>Particulate Energy (KeV)</th>
<th>Mean Range of Emission (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-emitters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodine-131</td>
<td>Beta, gamma</td>
<td>8.1 d</td>
<td>610</td>
<td>0.8</td>
</tr>
<tr>
<td>Yttrium-90</td>
<td>Beta</td>
<td>2.5 d</td>
<td>2,280</td>
<td>2.7</td>
</tr>
<tr>
<td>Rhenium-188</td>
<td>Beta, gamma</td>
<td>17 h</td>
<td>2,100</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Alpha-emitters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bismuth-213</td>
<td>1 Alpha, 2 beta, 1 gamma</td>
<td>46 min</td>
<td>8,400</td>
<td>0.05-0.08</td>
</tr>
<tr>
<td>Actinium-225</td>
<td>4 Alpha, 2 beta, 2 gamma</td>
<td>10 d</td>
<td>6,000-8,400</td>
<td>0.04-0.08</td>
</tr>
<tr>
<td>Astatine-211</td>
<td>1 Alpha, 1 gamma</td>
<td>7.2 d</td>
<td>6,800</td>
<td>0.04-0.10</td>
</tr>
</tbody>
</table>

Abbreviations: d, days; h, hours; min, minutes.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Phase of Study</th>
<th>Agent</th>
<th>Dose</th>
<th>Additional Therapy</th>
<th>Disease Status</th>
<th>No. of Patients</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jurcic</td>
<td>2002</td>
<td>I</td>
<td>$^{212}$Bi-lintuzumab</td>
<td>0.28-1 mCi/kg</td>
<td>None</td>
<td>Relapsed/refractory</td>
<td>18</td>
<td>14 patients with reductions in marrow blasts</td>
</tr>
<tr>
<td>Rosenblat</td>
<td>2010</td>
<td>I/II</td>
<td>$^{212}$Bi-lintuzumab</td>
<td>0.5-1.25 mCi/kg</td>
<td>Cytarabine</td>
<td>Untreated $\geq$ 60 yrs, relapsed/refractory</td>
<td>31</td>
<td>2 CRs, 2 CRp, 2 PRs</td>
</tr>
<tr>
<td>Jurcic</td>
<td>2011</td>
<td>I</td>
<td>$^{225}$Ac-lintuzumab</td>
<td>0.5-4 $\mu$Ci/kg</td>
<td>None</td>
<td>Relapsed/refractory</td>
<td>18</td>
<td>10 patients with reductions in marrow blasts; 3 with $\leq$ 5%</td>
</tr>
<tr>
<td>Jurcic</td>
<td>2013</td>
<td>I/II</td>
<td>$^{225}$Ac-lintuzumab</td>
<td>1-2 $\mu$Ci/kg (in 2 fractions)</td>
<td>LDAC</td>
<td>Untreated $\geq$ 60 yrs</td>
<td>7</td>
<td>4 patients with reductions in marrow blasts (mean, 58%) after cycle 1</td>
</tr>
</tbody>
</table>

Abbreviations: LDAC, low-dose cytarabine; CR, complete remission; CRp, CR with incomplete platelet recovery; PR, partial remission.
Targeted Alpha-Particle Immunotherapy for Acute Myeloid Leukemia

- FIG 1. Gamma camera images after partial cytoreduction of leukemic burden with cytarabine show targeting of 213Bi to marrow, liver, and spleen after the first injection (A) and blood pooling after the last (B). Rate images show uptake of 213Bi by bone marrow, liver, and spleen over 1 hour after the first injection (C) and clearance after the last (D), indicating saturation of CD33 sites within target organs. Originally published by the American Association for Cancer Research (Rosenblat TL et al. Clin Cancer Res. 2010;16:5303-5311.).

Bi-213&Ac-225 Abs for Acute Myeloid Leukemia
Pretargeting
Bispecific antibody + radiolabeled hapten
Higher tumor-to-normal

Hosono, Chatal et al. JNM 1997, 1998
Pretargeting

Feasibility of Affibody molecule-based PNA-mediated pre-targeting

Gamma-camera imaging of nude mice bearing HER2-expressing SKOV-3 xenografts at 1 h after injection of $^{111}$In-labelled agents

A. Conventional Affibody molecule $^{111}$In-DOTA-Z$_{HER2,556}$
B. $^{111}$In-DOTA-HP2 injected 4 h after pre-injection of Z$_{HER2,342}$-HP1;
C. $^{111}$In-DOTA-HP2 injected without pre-injection of Z$_{HER2,342}$-HP1.

Hadis Honarvar, Kristina Westerlund, Mohamed Altai, Mattias Sandström, Anna Orlova, Vladimír Tolmachev, Amelie Eriksson Karlström

EANM2015
Fukushima Medical University
Fukushima Global Medical Science Center
Targeted Alpha Therapy
Global Trends for Targeted Alpha Therapy
TAT-10

May 30-June 1, 2017, Kanawaza, Japan
RNT practices as a multidisciplinary team

- Nurses
- Technologists
- Clerks
- Pharmacists
- Medical Physicists
- Physicians

Patients
Summary

• RNT procedures with alpha-emitting or beta emitting nuclides are making remarkable progress across the globe.

• We should present radiological protection guidelines to disseminate and facilitate new technologies of RNT.
Thank you very much