New Treatment Facility and Targeted Alpha-particle Therapy in FMU

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Fukushima Global Medical Science Center

- Environmental Dynamics Examination Center
- Advanced Clinical Research Center
- Education & HR Development, Translational Research Center
- Fukushima “Life and Future” Medical Center
Current status of Fukushima Medical University in Radionuclide Therapy

• Perform approved radionuclide therapy
  • $^{131}$I therapy for differentiated thyroid cancer (DTC) and Graves’ disease
  • $^{90}$Y-anti-CD20 Ab for low-grade B-cell non-Hodgkin’s lymphoma (B-NHL)
  • $^{223}$Ra-chloride for symptomatic bone metastases with hormone refractory prostate cancer
  • $^{89}$Sr-chloride for relief of painful bone metastases
• Develop new radiopharmaceuticals for targeted radionuclide therapy
  • α, β-particle therapy
  • Produce $^{211}$At with in-house cyclotron (MP-30)
• Develop molecular imaging for radionuclide therapy
  • Companion diagnosis with PET/SPECT for targeted therapy
Domestic status of radionuclide therapy for DTC in Japan

(1) Increased performance
(2) Shortage of beds for therapy
(3) Long waiting period
(4) Poor survival

131I-MIBG therapy for malignant pheochromocytoma and paraganglioma in Japan

Summary

✓ Rarely “effective”
✓ Stable disease in majority
✓ Less side effects

Table 2
(A) Treatment-based response to 131I-MIBG radiotherapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheochromocytoma</td>
<td>0</td>
<td>1</td>
<td>40</td>
<td>9</td>
<td>50</td>
</tr>
<tr>
<td>Paraganglioma</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>1</td>
<td>54</td>
<td>10</td>
<td>65</td>
</tr>
</tbody>
</table>

CR, complete remission; MIBG, metaiodobenzylguanidine; PD, progressive disease; PR, partial remission; SD, stable disease.

Table 4
Details of bone marrow suppression in adult neuroendocrine tumors

<table>
<thead>
<tr>
<th>NCI toxicity grade</th>
<th>Thrombocytopenia</th>
<th>Anemia</th>
<th>Leukopenia</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>12</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>13</td>
<td>2</td>
<td>13</td>
</tr>
</tbody>
</table>

$^{131}$I-MIBG therapy for malignant pheochromocytoma in the USA

<table>
<thead>
<tr>
<th></th>
<th>Dose (mCi)</th>
<th>(mCi/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>492-1,160 (av. 818)</td>
<td>9-19</td>
</tr>
<tr>
<td>Total</td>
<td>492-3,191</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Total</th>
<th>2nd (vs 1st)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>CR</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>PR</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>MR</td>
<td>17</td>
<td>35</td>
</tr>
<tr>
<td>SD</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>PD</td>
<td>17</td>
<td>35</td>
</tr>
</tbody>
</table>

Survival (probability) vs Time (months)

Radionuclide therapy ward in Fukushima Medical University
Radionuclide therapy ward in Fukushima “Life and Future” Medical Center

37.0 GBq: (#3)
22.2 GBq: (#2)
7.4 GBq: (#4,5,6)
3.7 GBq: (#1,7,8,9)

Sufficient dose for efficacy
Theranostics = Therapy + Diagnostics

• Specific targets for radionuclide therapy
• Same target for diagnostic imaging
  • Indication
  • Therapeutic effectiveness and toxicity
  • Dosimetry
Clinical PET/CT and PET/MRI facility

- Blood analysis
- Operating
- Drug administration
- PET/MRI
- PET/CT
- Waiting room
PET/CT

Pancreas cancer

PET/CT

CT

PET/CT

Pancreas cancer

MRI

Diffusion weighted MRI

MRCP

Dilated main pancreatic duct

(Biograph mCT, Siemens)
PET/MRI

Undifferentiated pleomorphic sarcoma

Heterogeneous signal intensity on diffusion-weighted MRI

PET/MRI

Heterogeneously increased FDG uptake in the tumor

CT

Low density area in the right deltoid muscle

MRI

DWI

Heterogeneous signal intensity on diffusion-weighted MRI

T1WI
## Radionuclides for theranostics

<table>
<thead>
<tr>
<th>Radionuclides</th>
<th>$T_{1/2}$ (days)</th>
<th>Radiation</th>
<th>Radionuclides</th>
<th>$T_{1/2}$ (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{67}$Cu</td>
<td>2.58</td>
<td>$\beta^-$</td>
<td>$^{64}$Cu</td>
<td>0.53</td>
</tr>
<tr>
<td>$^{77}$Br</td>
<td>2.42</td>
<td>EC, Auger</td>
<td>$^{76}$Br</td>
<td>0.68</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>8.02</td>
<td>$\beta^-$</td>
<td>$^{124}$I</td>
<td>4.17</td>
</tr>
<tr>
<td>$^{177}$Lu</td>
<td>6.73</td>
<td>$\beta^-$</td>
<td>$^{68}$Ga</td>
<td>68 (min)</td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>0.3</td>
<td>$\alpha$</td>
<td>$^{124}$I</td>
<td>4.17</td>
</tr>
</tbody>
</table>
Characteristics of α-particle and β-particle

α-emitters are more capable comparing with β-emitters for therapy

➢ Increased cellular damage
  High LET (Linear energy transfer) : 97 (211At) vs. 0.2 keV/μm (90Y)
  High RBE (Relative biological effectiveness) : 5-20 (α) vs. 1 (β)

➢ Low toxicity
  Short path length : <100 μm (211At) vs. 11 mm (90Y)
  Limited radiation to adjacent normal organs, BM

<table>
<thead>
<tr>
<th>RI</th>
<th>Radiation</th>
<th>γ</th>
<th>T1/2</th>
<th>Energy (MeV)</th>
<th>Path length (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>67Cu</td>
<td>β</td>
<td>+</td>
<td>62.1 h</td>
<td>0.39</td>
<td>1.1</td>
</tr>
<tr>
<td>89Sr</td>
<td>β</td>
<td></td>
<td>50.5 d</td>
<td>1.49</td>
<td>8</td>
</tr>
<tr>
<td>90Y</td>
<td>β</td>
<td></td>
<td>64.1 h</td>
<td>2.28</td>
<td>11</td>
</tr>
<tr>
<td>131I</td>
<td>β</td>
<td>+</td>
<td>8.0 d</td>
<td>0.61</td>
<td>2</td>
</tr>
<tr>
<td>177Lu</td>
<td>β</td>
<td>+</td>
<td>6.7 d</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>211At</td>
<td>α</td>
<td>+</td>
<td>7.2 h</td>
<td>5.58</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>223Ra</td>
<td>α</td>
<td>+</td>
<td>11.4 d</td>
<td>26.5</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>
Characteristics of MP-30 Cyclotron

Special Features:
- Vertical Irradiation System
- Automatic Target Transport System

Advantage of vertical irradiation system
→ Easy material fixing
  for low melting point target materials
  ex. Gallium, Bismuth
for powder or lump target materials
  ex. Oxide, Enrichment powder
Production of $^{211}\text{At}$ with MP-30 Cyclotron

Should be less than 28 MeV
Not to be contaminated with $^{210}\text{At} \rightarrow ^{210}\text{Po}$ (Highly radiotoxic)

- $^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$
- $^{209}\text{Bi}(\alpha, 3n)^{210}\text{At}$

Beam current 20 μA

Bismuth lump (Target material)
Niobium body
Aluminum foil (Degrader & Sealer)
Water cooled
He
<28 MeV beam
32 MeV beam

Production of $^{211}\text{At}$ with MP-30 Cyclotron

Beam current 20 μA
Production of At-211 at Fukushima Medical University

At-211 production

$^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$

Projectile energy <28 MeV

Approximately 1.5 GBq (EOB) of $^{211}\text{At}$

No production of At-210

MP-30, Sumitomo Heavy Industry

$^{211}\text{Po}$ $^{211}\text{At}$ $^{211}\text{Po}$

γ-ray spectrometry analysis
Hot labs: Production of radioactive compound and quality control

Chemical black box (Automatic synthesis device)

Quality control device
Animal facility for preclinical study with radionuclide imaging.
Animal breeding facilities

- Three breeding rooms including quarantine inspection room
- Isolated 240 cages for rodent

Automatic cage washer

Autoclave

Isolated housing
Cell culture equipment

- CO₂ incubator
- Safety cabinet
- Microscope, cell counter

- Cell culture for in vitro exam and preparation for tumor model in immunodeficiency mice
- Specific pathogen free status is secured
Radioactivity measurement and analyses

- Liquid scintillation counter
- Gamma counter
- Fluorescence and luminescence microscope
- HPLC for radioactive compounds

- High spec analytical instruments for radioactive compounds and their metabolites
- Pharmacokinetic and pharmacodynamic study for drug development
Imaging apparatus for small animal

- Molecular imaging apparatus can be used for in vivo analysis of radioactive compounds
- Pharmacokinetic and pharmacodynamic study for drug development
Development of novel radionuclide therapy in Fukushima

• Develop new treatment
  • Investigate target-oriented therapeutic strategy
  • Produce novel radiolabeled compounds
  • Preclinical study and clinical trials for approval
• Targeted α-particle therapy
  • $^{211}$At-labeled compounds
  • Stable and constant production with safety
• Collaboration with researchers, clinical practitioners
• Cooperation with pharmaceutical companies, machinery companies
Thank you for your attention