The Case for Dosimetry in Alpha-Emitter Therapy

George Sgouros, Ph.D.
Russell H. Morgan Dept of Radiology & Radiological Science
Johns Hopkins University, School of Medicine
Baltimore MD
Consultant: Bayer
Scientific Advisory Board: Orano Med
Founder: Radiopharmaceutical Imaging and Dosimetry (Rapid), LLC
## Current cancer therapies

### 5-year survival by stage*

<table>
<thead>
<tr>
<th>Site</th>
<th>localized</th>
<th>distant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>99%</td>
<td>30%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>90%</td>
<td>14%</td>
</tr>
<tr>
<td>Lung</td>
<td>56%</td>
<td>5%</td>
</tr>
<tr>
<td>Ovary</td>
<td>93%</td>
<td>29%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>32%</td>
<td>3%</td>
</tr>
<tr>
<td>Prostate</td>
<td>100%</td>
<td>30%</td>
</tr>
</tbody>
</table>

*SEER.Cancer.gov
Current cancer therapies

After the cancer has spread/metastasized

• Chemotherapy
  - Kill rapidly proliferating cells

• Targeted Biologic Therapy (hormonal Tx)
  - Inhibit signaling pathways that tumor cells are addicted to (i.e., rely on to maintain cancer phenotype)

• Immunotherapy
  - Overcome immune tolerance to cancer

• Radiopharmaceutical Therapy
  - Kill targeted cells by localized radiation delivery
## Radiopharmaceutical therapy

<table>
<thead>
<tr>
<th>RPT agent</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{131}$I-radioiodine</td>
<td>Malinckrodt/Jubil. Draximage</td>
<td>Thyroid cancer</td>
</tr>
<tr>
<td>$^{131}$I-MIBG</td>
<td>Progenics</td>
<td>Adrenergic$^+$ tumors</td>
</tr>
<tr>
<td>$^{212}$Pb-trastuzumab</td>
<td>OranoMed</td>
<td>HER2$^+$ tumors</td>
</tr>
<tr>
<td>$^{212}$Pb-PRIT</td>
<td>OranoMed/Roche</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>$^{212}$Pb-antisomatostatin</td>
<td>OranoMed/Radiomedix</td>
<td>Somatostatin$^+$ tumors</td>
</tr>
<tr>
<td>$^{212}$Pb-aTEM1</td>
<td>OranoMed/Morphotek</td>
<td>TEM1$^+$ tumors</td>
</tr>
<tr>
<td>$^{212}$Pb-aCD37</td>
<td>OranoMed/NordicNanovector</td>
<td>Leukemia</td>
</tr>
<tr>
<td>$^{131}$I-aCD45</td>
<td>Actinium Pharmaceuticals</td>
<td>BM xplant prep</td>
</tr>
<tr>
<td>$^{225}$Ac-aCD33</td>
<td>Actinium Pharmaceuticals</td>
<td>Leukemia</td>
</tr>
<tr>
<td>90Y-microspheres</td>
<td>Varian/Sirtex</td>
<td>Hepatic malignancies</td>
</tr>
<tr>
<td>90Y-microspheres</td>
<td>BTG</td>
<td>Hepatic malignancies</td>
</tr>
<tr>
<td>RPT agent</td>
<td>Company</td>
<td>Indication</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Lutathera (177Lu)</td>
<td>Novartis/AAA</td>
<td>Somatostatin+ tumors</td>
</tr>
<tr>
<td>177Lu-aPSMA-R2</td>
<td>Novartis/AAA</td>
<td>Prostate, tumor neovasc.</td>
</tr>
<tr>
<td>177Lu-NeoBOMB1</td>
<td>Novartis/AAA</td>
<td>Bombesin+ tumors</td>
</tr>
<tr>
<td>177Lu-PSMA-617</td>
<td>Endocyte</td>
<td>Prostate, tumor neovasc.</td>
</tr>
<tr>
<td>Xofigo (223Ra)</td>
<td>Bayer</td>
<td>Bone mets</td>
</tr>
<tr>
<td>HER2-TTC (227Th)</td>
<td>Bayer</td>
<td>HER2+ tumors</td>
</tr>
<tr>
<td>PSMA-TTC (227Th)</td>
<td>Bayer</td>
<td>Prostate, tumor neovasc.</td>
</tr>
<tr>
<td>MSLN-TTC (227Th)</td>
<td>Bayer</td>
<td>Mesothelin+ tumors</td>
</tr>
<tr>
<td>aCD22-TTC (227Th)</td>
<td>Bayer</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>FPX-01 (225Ac)</td>
<td>J&amp;J/Fusion Pharma</td>
<td>NSCLC, pan-cancer target</td>
</tr>
</tbody>
</table>
Radiopharmaceutical therapy

- 21 RPTs (abridged list)
- 5 commercially available/FDA approved
  - $^{131}$I thyroid malignancies
  - Xofigo ($^{223}$Ra) castration resistant prostate cancer bone mets
  - Lutathera ($^{177}$Lu) somatostatin+ tumors
  - Sirtex ($^{90}$Y) hepatic malignancies
  - Therapsheres ($^{90}$Y) hepatic malignancies
- 3 beta-emitters – $^{131}$I, $^{177}$Lu, $^{90}$Y
- 4 alpha-emitters – $^{225}$Ac, $^{227}$Th, $^{212}$Pb/$^{212}$Bi, $^{223}$Ra
Clustered ionizations from low-energy electron

Single ionization

-- high probability of damage when alpha-particle hits DNA.

Delta-ray electron

Alpha Radiobiology

- double stranded DNA breaks
- no resistance
- no oxygen effect
- no dose-rate effect
Relative Biological Effectiveness (RBE)

- dose for cell kill w/ betas ≈ 3-7 x alphas, *in vitro*

\[ RBE(x) = \frac{D_r(x)}{D_t(x)} \]

- Biological end-point
- Reference radiation
- Dosimetry methodology

\( x = \) biological effect, \( r = \) reference radiation, \( t = \) test radiation
<table>
<thead>
<tr>
<th>Agent, manipulation</th>
<th>$D_0$ (Gy)</th>
<th>RBE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{213}$Bi-Rituximab (irrelevant Ab)</td>
<td>0.84</td>
<td>3.8</td>
</tr>
<tr>
<td>$^{213}$Bi-Cetuximab</td>
<td>0.87</td>
<td>3.7</td>
</tr>
<tr>
<td>$^{213}$Bi-Cetuximab, siRNA scrambled control</td>
<td>0.69</td>
<td>4.7</td>
</tr>
<tr>
<td>$^{213}$Bi-Cetuximab, siRNA DNA-PKcs-/-DNA-PKcs-</td>
<td>0.37</td>
<td>8.6</td>
</tr>
<tr>
<td>$^{213}$Bi-Cetuximab, siRNA BRCA1-/-BRCA1-</td>
<td>0.21</td>
<td>15.6</td>
</tr>
</tbody>
</table>

*RBE is reported using 37% cell survival as the biological endpoint and Cs-137 gamma rays as the reference radiation.*

Song, et al. MCT 2013
Efficacy of Radium-223 in Bone-metastatic Castration-resistant Prostate Cancer with and Without Homologous Repair Gene

Table 1 – List of pathogenic homologous recombination deficiency (HRD) mutations

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Gene</th>
<th>Origin of mutation</th>
<th>Amino acid change</th>
<th>Nucleotide change</th>
<th>Mutation mechanism</th>
<th>Type of analysis</th>
</tr>
</thead>
</table>

Graphs:
- Time to alkaline ph
- Overall survival by HRD status
- Number at risk
- Therapeutic efficacy by HRD status
Radioactive chemotherapy

Pharmacodynamic study
- Utilization/metabolism
- Early stage in development

of no use after drug development
- Treat empirically
- Clinical trials to find optimum

Systemic Radiation Delivery

Essential to implementing patient therapy

Only if validated and found to impact treatment outcome
Biomarkers

- Select patients most likely to respond
- Avoid toxicity
- Tumor biopsy
- Serum sampling
- Genetic and epigenetic marker analysis
- Must be rigorously qualified/validated retrospectively or in prospective studies
- Standardized
- Incorporated in the design of clinical trials
Dosimetry

- Select patients most likely to respond
- Avoid toxicity
- Tumor biopsy
- Serum sampling
- Genetic and epigenetic marker analysis
- Must be rigorously qualified/validated retrospectively or in prospective studies
- Standardized
- Incorporated in the design of clinical trials
Example of patient variability

Previously demonstrated that 75 cGy to WB increases RM toxicity

Is small fraction of patients that will be undertreated worth the dosimetry effort/cost?
Red Marrow Dose vs Response: Literature

Platelet Toxicity Grade

- A (N = 109)
- B (N = 57)
- C (N = 91)
- D (N = 56)

O’Donoghue, et al., CBR ’00
Patients with advanced midgut neuroendocrine tumors who have had disease progression during first-line somatostatin analogue therapy have limited therapeutic options. This randomized, controlled trial evaluated the efficacy and safety of lutetium-177 (177Lu)–Dotatate in patients...
• Early phase trials – opportunity to collect data
• Don’t propose altering treatment
• Show that dosimetry would have predicted toxicity or lack of efficacy
• Assess patient variability
• Apply rigorous, consistent methods
  - 3 time-points; 1st and last cycle
  - Pre-therapy tracer study
  - SPECT/CT
• Use collected data to validate simpler schemes
• Be prepared to accept conclusions
  - Prior patient history, dose-range can impact dose-response relationship
Modeling impact of tumor burden on targeting

- Impact of tumor burden on RPT PK, normal organ, tumor absorbed dose
- Adjust admin. activity
- RPT is inherently a precision medicine modality
- Do better than radioactive chemotherapy
- Focus model on disseminated (i.e., rapidly accessible) disease
Leukemia Targeting Model - Antibody

Plasma vol. + ECF of liver, spleen and RM

1 Ab \[\xrightarrow{k(0,1)}\] 2 AbAg \[\xrightarrow{k(1,2)}\] 3 AbAg_i

\[\xrightarrow{k(2,1)}\] \[\xrightarrow{k(3,2)}\] \[\xrightarrow{k(0,3)}\]
Leukemia Targeting Model – $^{225}\text{Ac}$-Antibody

**Tissue absorbed dose vs target cell number**

- **Marrow**: $10^9$
- **Kidneys**: $10^{10}$
- **Liver**: $10^{11}$
- **Lungs**: $10^{12}$

**Tissue absorbed dose (mGy/MBq)**

- marrow: 1000, 2000, 3000, 4000
- kidneys: 1000, 2000, 3000
- liver: 1000, 2000
- lungs: 1000
Modeling cell kill in RPT

\(N_c\) - non-radioactive (cold) cells;
\(N_h\) - radiolabeled (hot) cells;

\(k_+\) - Ab-Ag association rate (nmol\(^{-1}\) h\(^{-1}\))

\(k_-\) - Ab-Ag dissociation rate (h\(^{-1}\))

\(\lambda_{bio}\) - Ab loss due to biological clearance (h\(^{-1}\))

\(\kappa\) - cell kill rate (h\(^{-1}\))

\(\gamma\) - growth rate (h\(^{-1}\))

\(\delta\) - cell loss rate (h\(^{-1}\))
Animal Model: LCV injection

nude mice, $10^5$ NT2.5Luc+ cells

$T_d = 1 \text{ d}$
Mouse Survival Data

Fraction of Survived Mice vs. Time (Days)

- Control, n=18
- 120µCi 7.16.4-Bi-213, n=28
- 90µCi 7.16.4-Bi-213, n=9

Song, et al. Clin Cancer Res '08
Mouse Data

Song, et al. Clin Cancer Res ’08
Simulation Results

Total Number of Tumor Cells vs. Days

- Untreated
- Bi-213, 120 microCi
## Simulation Results

<table>
<thead>
<tr>
<th>Tumor cells inoculated</th>
<th>Radionuclide</th>
<th>Administered Activity</th>
<th>Survival Time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median (measured)</td>
<td>From model</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$10^4$</td>
<td>Untreated</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>$10^4$</td>
<td>$^{213}$Bi</td>
<td>4.44 MBq (120 µCi)</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31.5</td>
</tr>
<tr>
<td>$10^5$</td>
<td>Untreated</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>$10^5$</td>
<td>$^{213}$Bi</td>
<td>3.33 MBq (90 µCi)</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37.6</td>
</tr>
<tr>
<td>$10^5$</td>
<td>$^{225}$Ac</td>
<td>11.1 kBq (300 nCi)</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>42.8</td>
</tr>
<tr>
<td>$10^5$</td>
<td>$^{225}$Ac</td>
<td>14.8 kBq (400 nCi)</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47.8</td>
</tr>
</tbody>
</table>

*10^8 cells = kill line = median survival time*
Conclusions

- RPT dosimetry has potential to reduce empiricism
- Mechanism of action is well understood
- Needed measurements are known
- Patient-specific dosimetry tools are available
- Response data from radiotherapy
- Can measure delivery of the therapeutic agent to tumor targets and to normal organs
- Calculate radiation dose to tumors, normal organs
- Guide escalation protocols and plan treatment

Implement standardized, validated activity quantification and dosimetry methods in early phase clinical trials to gather rigorous evidence that dosimetry will improve patient care.
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