Radioimmunotherapy: recent advances and current opportunities

Thursday October 5, 2017
Conflict of interest

No relevant affiliations or financial involvement with any organization, company or entity with financial interest in RIT.

Scientific interest:  

- CHU de Nantes  
  Nantes University Hospital: Clinical trial in RIT

- ARRONAX Cyclotron: Production of innovative isotopes ($^{64}$Cu, $^{211}$At)  
  And Radiopharmacy unit of Nantes University Hospital

- French National Institute of Health and Medical Research  
  Nantes Cancer Research Center

- Team #13: Nuclear Oncology  
  Searching field:  
  - RIT (α, β$^-$), Radiopeptide therapy, phenotypic imaging,...  
  - Interdisciplinary aspect: radiobiology, immunology, radiochemistry, radiopharmacy, radiophysics,...  
  - Transfer from laboratory to patient (clinical trial in hospital Nuclear Medicine department)
Historical context of Radio-ImmunoTherapy (RIT)

- Classical nonspecific cytotoxic chemotherapies
- Targeted therapies

Köhler & Milstein
Nobel prize 1984

Monoclonal Antibodies
*Nature 1975*
Historical context of Radio-ImmunoTherapy (RIT)

Radioimmunotherapy (RIT)

1978 – CarcinoEmbryonicAntigen as a target for detection (Diagnostic application) with $^{131}$I-mAb.
Goldenberg D. New England Journal of Medicine
1987 – Therapy of B-cell Lymphoma (Therapeutic application) with $^{131}$I-mAb.
DeNardo S.J. Int. J. Biol. Markers

Radiotherapy pioneers: C. Regaud & A. Lacassagne (1926)
“The ideal agent to treat cancer will be constituted by heavy elements, able to emit some radiation ... to destroy cancer cells”

... Still in progress
RIT principle

Specific antigen

Cancer cell

mAb = specific vector for cancer cell
*i.e.* specific irradiation of tumor cell

Specific irradiation
= goal of RIT (better effect with long accumulation time)

Non specific irradiation
= adverse event (less with shorter circulation time and high clearance from healthy tissue)
**RIT principle**

Specific antigen

Cancer cell

mAb = specific vector for cancer cell
\( i.e. \) specific irradiation of tumor cell

Specific irradiation
= goal of RIT (better effect with long accumulation time)

Key of success:
Good contrast between healthy and cancer tissue

Risk

Benefit

Non specific irradiation
= adverse event (less with shorter circulation time and high clearance from healthy tissue)
RIT principle

- **Specific antigen**
- **Cancer cell**

- **mAb = specific vector for cancer cell**
  - *i.e. specific irradiation of tumor cell*

  - **Irradiation of tumor cell = OK**
  - **Irradiation of healthy cell = BAD**

  - **Irradiation of distant cell (no fixation of mAb) = Cross fire effect = OK**

For many years: Haematological disease...
Current limitations of RIT

Abnormal 3D tumor neovasculature
Stenosis (→), Arteriovenous shunt, blood flow inversion, dead end (○),...

Neoangiogenesis > Neolymphogenesis ➞ High Interstitial pressure

Limitation for passive diffusion (Fick’s principles)

Current limitations of RIT ...or not

**Abnormal 3D tumor neovasculature**
Stenosis (→), Arteriovenous shunt, blood flow inversion, dead end (●),...

Neoangiogenesis > Neolymphogenesis → **High Interstitial pressure**

Limitation for passive diffusion (Fick’s principles)

In practice, this poor limitation seems to be overestimated

**Autoradiographic study with $^{125}$I-mAb**

1 h post I.V.  6 h post I.V.  7 d post I.V.

**The diffusion is more slowly but sufficient for a good tumor irradiation by RIT**

Optimisation way (if necessary): co-infusion with interleukin-2, chemical modification of mAb, positive pressure injection (see « injection way » slide),...
Current limitations of RIT ...or not (⚠️ items that need to pay particular attention)

Irradiation parameters of RIT

**External beam radiotherapy**
- High dose rate / Short time (relatively)
- Well known radiobiology effect

**Radioimmunotherapy**
- Low dose rate / Long time (kinetic of the mAb)
- Unperfect known radiobiology effect...
  - Dose response relationship ?
  - Cell survival ?

Supply chain of radionuclides (Stumbling points)

**Isotope choice:** emitter type, half-life, energy,..

**Production:** cost & availability

**Chemical process:** Specific activity, radionuclide purity, radiolabelling yield, radiochemical purity, ...

**Radiopharmaceutical quality**
Recent advances in RIT: mAb derivatives

1st mAb: Murine origin (high immunogenicity)

Ag recognition (hypervariable regions – CDR)
- Monospecific
- Divalent
- High affinity (Kd ≈ 10^{-9} M)

Relatively former evolution (for RIT middle 2000’s):

Modification of mAb (Biochemist and immunochemist current work)

Reduction of half-life and kidney elimination
Recent advances in RIT: mAb derivatives

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Recent advances in RIT: mAb derivatives

Relatively former evolution (for RIT middle 2000’s):

- Immunogenicity
- Pharmacokinetic half-life

Modification of mAb (Biochemist and immunochemist current work)

Reduction of half-life and kidney elimination

- Mainly for diagnostic purpose

- Used for RIT purpose: Clinical trial in Ovarian Carcinoma
  - High efficacy, Renal side effects tolerable
  
Recent advances in RIT: Pretargeting

Affinity Enhancement System (AES)

1st step: IV injection of bispecific antibody

- Bispecific mAb (affinity for tumor antigen + specific hapten)
  - Non radioactive
  - Slow clearance

... wait for the full elimination of bispecific mAb
Recent advances in RIT: Pretargeting

Affinity Enhancement System (AES)

2nd step: IV injection of Radioactive hapten

radioactive
Fast clearance
Affinity for the 2\textsuperscript{nd} valence of the bispecific mAb

Rapid Renal Elimination = low toxicity

Clinical validations:
**Medullary thyroid carcinoma**: mAb anti-CEA x antiDTPA-TL-In
Delay between mAb (75mg/m\textsuperscript{2}) and hapten (1.8 GBq/m\textsuperscript{2}) injection = 5 days

**Results:** long term disease stabilisation (RECIST Criteria) and minor toxicity (transient grade I-II hepatic toxicity + grade III-IV leukopenia & thrombopenia)

Recent advances in RIT: Radiosensitization

Goal: potentiate the therapeutic action of RIT

Topoisomerase I inhibitor (Topotecan)
Breast cancer
*Ng B. et al. Cancer Res. 2001*

Pyrimidine analogs (Gemcitabine)
Pancreatic cancer

Anthracyclin compound (Doxorubicin)
Multiple myeloma

Taxol derivatives (Paclitaxel®)
Epidermoid carcinoma

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Preclinical proof: Co-administration of «cold» drug & RIT = Synergic effect
Recent advances in RIT: Radiosensitization

**Goal:** potentiate the therapeutic action of RIT

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Pancreatic cancer

 Anthracyclin compound (Doxorubicin)
Multiple myeloma

Taxol derivatives (Paclitaxel®)
Epidermoid carcinoma

Proteasome inhibitor (Bortezomib®)
Non-Hodgkin Lymphoma

Preclinical proof: Co-administration of « cold » drug & RIT = Synergic effect

Clinical proof: Phase I (toxicological study)
*To be continued...*
# Recent advances in RIT: Innovative radionuclides

**Radioisotope choice** (non-exhaustive...):

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
<th>Decay mode</th>
<th>Energy (keV)</th>
<th>Range (mm)</th>
<th>Other emission</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{125}$I</td>
<td>59.4 d</td>
<td>Auger $e^-$</td>
<td>3.2</td>
<td>22.7</td>
<td>≈ 10 nm</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>8.02 d</td>
<td>$\beta^-$</td>
<td>191.6</td>
<td>606.3</td>
<td>0.4</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>64.0 h</td>
<td>$\beta^-$</td>
<td>933.7</td>
<td>2280.1</td>
<td>4.2</td>
</tr>
<tr>
<td>$^{177}$Lu</td>
<td>6.65 d</td>
<td>$\beta^-$</td>
<td>149.3</td>
<td>498.3</td>
<td>0.3</td>
</tr>
<tr>
<td>$^{67}$Cu</td>
<td>61.83 h</td>
<td>$\beta^-$</td>
<td>189</td>
<td>561.7</td>
<td>0.27</td>
</tr>
<tr>
<td>$^{186}$Re</td>
<td>3.72 d</td>
<td>$\beta^-$</td>
<td>359.2</td>
<td>1069.5</td>
<td>0.9</td>
</tr>
<tr>
<td>$^{188}$Re</td>
<td>17.0 h</td>
<td>$\beta^-$</td>
<td>795.41</td>
<td>2120.4</td>
<td>3.5</td>
</tr>
<tr>
<td>$^{225}$Ac</td>
<td>9.92 d</td>
<td>$4 \alpha$</td>
<td>5792 - 8375</td>
<td>&lt; 0.1</td>
<td></td>
</tr>
<tr>
<td>$^{213}$Bi</td>
<td>45.6 min</td>
<td>$\alpha$</td>
<td>5549 - 8375</td>
<td>&lt; 0.1</td>
<td></td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>7.214 h</td>
<td>$\alpha$</td>
<td>5869 - 7450</td>
<td>&lt; 0.1</td>
<td></td>
</tr>
</tbody>
</table>

- **Chemical properties for radiolabeling**
- **Emission type** (Radiobiological mechanism)
- **Energy and pathlength**: Energy deposition in matter, ionisation density
- **Relative Biological Effectiveness (RBE)** and Linear Energy Transfer (LET)
- **Image possibility** (biodistribution following, dosimetry,...)
- **Compatibility with mAb pharmacokinetic** (residence time in tumor)
Recent advances in RIT: Innovative radionuclides

Alpha or bêta minus?

Couturier O. et al. EJNM 2005. 5: 601-614
Recent advances in RIT: Innovative radionuclides

**β-**
- **131I**
  - Total: 2878 items
- **90Y**
  - Total: 1677 items
- **177Lu**
  - Total: 188 items

**α**
- **211At**
  - Total: 116 items
- **225Ac**
  - Total: 49 items
- **213Bi**
  - Total: 71 items

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Total</th>
<th>Trend</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>131I</strong></td>
<td>2878</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td><strong>90Y</strong></td>
<td>1677</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td><strong>177Lu</strong></td>
<td>188</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td><strong>211At</strong></td>
<td>116</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>225Ac</strong></td>
<td>49</td>
<td>3-4 items/year</td>
<td></td>
</tr>
<tr>
<td><strong>213Bi</strong></td>
<td>71</td>
<td>4-5 items/year</td>
<td></td>
</tr>
</tbody>
</table>
Recent advances in RIT: Innovative radionuclides

α Efficacy – Proof of concept

18 patients:
14 with multiform glioblastoma (GBM)
3 with anaplastic oligodendroglioma
1 with anaplastic astrocytoma
71 - 347 MBq of 81C6 - $^{211}$At

Zalutsky et al. J Nucl Med (49)2008 30-38

<table>
<thead>
<tr>
<th>Toxicity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic anemia (grade 4); seizures (grade 3)</td>
</tr>
<tr>
<td>Hand numbness (grade 2; resolved)</td>
</tr>
<tr>
<td>Seizures (grade 3); headache (grade 2; resolved)</td>
</tr>
<tr>
<td>Seizures (grade 3)</td>
</tr>
<tr>
<td>Seizures (grade 2); headache (grade 2; resolved); visual field loss (grade 2)</td>
</tr>
<tr>
<td>Aphasia (grade 2; resolved)</td>
</tr>
<tr>
<td>Seizures (grade 4)</td>
</tr>
<tr>
<td>Headache (grade 2; resolved)</td>
</tr>
<tr>
<td>Seizures (grade 2)</td>
</tr>
</tbody>
</table>
Recent advances in RIT: Injection way

Classical way: I.V.
Pharmacokinetic limit of mAb
Intratumoral penetration
« Contrast » notion:
Tumor/Healthy tissue ratio

Alternative way: I.P.
Used mainly for ovarian and colorectal cancer

Alternative way: Post-surgical cavity
Convection Enhanced Delivery (CED)
Validation for peptide, future for mAb?
1 clinical trial in literature = acceptable safety profile...

Dose to tumor
Large impact of biodistribution
Critical organ

peritoneal carcinomatosis of colon cancer
Better accessibility to metastases

Drug concentration
Distance from injection site

Convection
Diffusion
Recent advances in RIT: Dose fractionation approach

RIT principal limitation: bone marrow / haematological toxicity

If only 1 injection: dose limitation to circumvent the toxicity...

Idea: use fractionated dose like external radiotherapy (increment of total dose)
Principe: bone marrow regenerate faster than tumor cell

\[ \text{177Lu-Anti-PSMA antibody} \]

\[ \text{Batra J.S. et al. J. Urol. 2016} \]

Single dose RIT: 2400-2600 MBq/m\(^2\)
Fractionated dose RIT: 2960 MBq/m\(^2\)  \(\approx +20\%\)
Increase of overall survival
**Conclusion: Current opportunities**

**Current status**
- Haematologic tumors
- Solid tumors

Clinical proof of efficacy

**Recent advances**
(radionuclides, mAb bioengineering, radiopharmaceutical development, protocol methodology, microenvironment targeting,...):

- Major evolution: Increase efficacy
- Decrease toxicity (mainly haematological)

**For tomorrow...**

- Old R&D industrial antibodies (no intrinsic cytotoxicity but good vector properties)
- Radiochemistry and radiopharmaceutical development
- Scaffold proteins ?
- Liposomal formulation (increase of the Specific Activity)
- Microenvironment targeting (PD-L1 status ?)
- Contribution of phenotypic imaging as companion diagnostic tool
- Combination between RIT and active immunotherapy (renewal of abscopal effect ?)

...**Preliminary clinical results appears promising...**

...personal medicine for RIT is almost a reality
Thank you for your attention