Targeted Radioimmunotherapy and Theranostics

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Disclosures

• Consultant/Advisory board/Honoraria (Current/Past): Ymabs; Progenics, Bayer, Medimmune/AZ

• Sponsored trials/Research support: Imaginab, Genentech, Actinium pharma/fluropharma
Overview

• Advantages of alpha emitters
• Radioimmuno targeted therapy
  • Concepts
  • Advantages and Limitations
• Radioimmunotargets and Clinical studies
• Methods to improve radioimmunotargeted delivery
  • Compartmental
  • Intratumoral
  • Pretargeted delivery
• Clinical trials
Crossfire Enhances Antibody Action

Naked Antibody or Ab drug conjugates

Radiolabeled Antibody
Alpha emitters and Radioimmunotherapy

- Specificity
- High LET radiation
- To deliver a lethal dose preferentially to those cells expressing higher concentration of the target
- Lower toxicity to adjacent normal tissue
- Depends on
  - Affinity
  - Antigen concentration
  - Vascularity
  - Antibody/antigen rate contrasts
Challenges

• Radioactive daughters
• Long half life of antibodies- kinetics
• Blood and organ dosimetry
• Imaging- ? Imageable gamma emissions
Challenges

• Tumor penetration
• Heterogeneity
• Dose delivery
  • Internalizing vs noninternalizing
  • Bulky tumors
  • Antigenic expression
  • Vascularity
Imaging:

Bone Scan  223 RaCl2
Time course of radiolabeled antibody uptake

AUC tumor/blood from 3:1 to 6:1

Long Blood Clearance Times or biological T1/2
Dosimetry for αRIT

• Bone marrow: common dose limiting
  • Tolerance: 2-3 Gy
  • Less critical for leukemias.
  • Localized/compartamental therapies.
• Organ and Tumor dosimetry: Critical but a challenge
Administered activities of $^{90}$Y-J591 projected to result in a red marrow absorbed dose of 1.85Gy and corresponding estimates of average absorbed doses to liver and lesions for these administered activities.

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Biodistribution

Antibody Mass Escalation Study in Patients with Castration-Resistant Prostate Cancer Using $^{111}$In-J591: Lesion Detectability and Dosimetric Projections for $^{90}$Y Radioimmunotherapy

Necat Pandit-Taskar1,2, Joseph A. O’Donoghue1, Michael J. Morris2,3, Eize A. Wills2, Lawrence H. Schwartz1, Mithat Gonen5, Howard I. Scher3,5, Steven M. Larson1,2, and Chattanya R. Divgi1,2

10 mg  25 mg  50 mg  100 mg
Antibody Mass Escalation Study in Patients with Castration-Resistant Prostate Cancer Using $^{111}$In-J591: Lesion Detectability and Dosimetric Projections for $^{90}$Y Radioimmunotherapy

Neeta Pandit-Tasekar1,2, Joseph A. O’Donoghue1, Michael J. Morris4,5, Erez A. Wills6, Lawrence H. Schwarte1, Mithat Gomer7, Howard I. Scher4,7, Steven M. Larson1,2, and Chaitanya R. Divgi1,2

Administered Activities of $^{90}$Y-J591 and Corresponding Estimates of Average Absorbed Doses

<table>
<thead>
<tr>
<th>Administered antibody mass</th>
<th>10 mg</th>
<th>25 mg</th>
<th>50 mg</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity of $^{90}$Y for red marrow absorbed dose of 1.85 Gy (MBq)</td>
<td>3340</td>
<td>2520</td>
<td>2140</td>
<td>2060</td>
</tr>
<tr>
<td>Projected absorbed dose to liver (Gy)</td>
<td>19.9</td>
<td>10.3</td>
<td>7.2</td>
<td>5.1</td>
</tr>
<tr>
<td>Projected absorbed dose to lesions (Gy)</td>
<td>193</td>
<td>195</td>
<td>208</td>
<td>196</td>
</tr>
</tbody>
</table>
Phase I Trial of 225Ac–J591 in Patients With mCRPC NCT03276572

• Open-label, single-center
• Phase I dose escalation study
  • Determine dose-limiting toxicity (DLT) and
  • The maximum tolerated dose (MTD) of 225Ac–J591 in a single dose regimen.
• Progressive mCRPC: i. PSA progression ii. Objective radiographic progression in soft tissue iii. New bone lesions
• N=42
Preoperative characterisation of clear-cell renal carcinoma using iodine-124-labelled antibody chimeric G250 ($^{124}$I-cG250) and PET in patients with renal masses: a phase I trial

Phase 2 Study of Lutetium 177–Labeled Anti–Carbonic Anhydrase IX Monoclonal Antibody Girentuximab in Patients with Advanced Renal Cell Carcinoma

Leucocyte counts during RIT cycles 1 and 2

Thrombocyte counts during RIT cycles 1 and 2

? Preclinical evaluation of Actinium 225-Girentuximab-Theranostic imaging: 89 Zr-Girentuximab

E J Urol 2016
Localized – compartmental therapies

• Ideal for small volume disease / Micrometastasis
• Disseminated disease within the compartment
• Intratumoral-
  • Surgically unresectable/ recurrent disease not amenable to other treatments
  • Disadvantage: Invasive
Intra-Ommaya antibody $^{131}$I-8H9 (omburtumab) or $^{131}$I-3F8

Kramer K et al J Neurooncol, 2010
Convection-enhanced delivery for diffuse intrinsic pontine glioma: a single-centre, dose-escalation, phase 1 trial


Lancet 2018
Multi-step Targeting

**STEP 1**
Tumor targeting

**STEP 2**
Blood clearance at peak mAb uptake

**STEP 3**
Radiolabeling

*SA  MAb-Streptavidin  ♦ Clearing agent  *-B  90Y-DOTA-biotin*
Leveraging bioorthogonal click chemistry to improve 225Ac-radioimmunotherapy of pancreatic ductal adenocarcinoma

Sophie Poty, Lukas M Carter, Komal Mandleywala, et al.

Figure 5

- **Treatment**:
  - $^{225}$Ac-DOTA-PEG$_2$-SB1 (37 kBq)
  - SB1-TCO + $^{225}$Ac-DOTA-PEG$_2$-Tz (37 kBq)
  - Control: Saline (Vehicle)

- **Graphs**:
  - Panel a: percent survival over days
  - Panel b: survival by days
  - Panel c: body weight, RBC, HCT, WBC, PLT over days
Sequential Cytarabine and α-Particle Immunotherapy with Bismuth-213–Lintuzumab (HuM195) for Acute Myeloid Leukemia

Todd L. Rosenblat¹, Michael R. McDevitt¹, Deborah A. Mulford¹, Neeta Pandit-Taskar¹, Chaitanya R. Divgi¹, Katherine S. Panageas¹, Mark L. Heaney¹, Suzanne Chanel¹, Alfred Morgenstern², George Sgouros¹, Steven M. Larson¹, David A. Scheinberg¹, and Joseph G. Jurcic¹

Fig. 1. Percentage change in bone marrow blasts after treatment with sequential cytarabine and 213Bi-lintuzumab in 26 evaluable patients.

Fig. 2. Kaplan-Meier plot showing the probability of survival for patients with previously untreated AML and those with relapsed or refractory disease.
Preclinical development of CD38-targeted $^{89}$Zr-daratumumab for imaging multiple myeloma and Actinium-225 Daratumumab for TAT

A. Representative maximum intensity projection (MIP) coronal and axial $^{89}$Zr-daratumumab/PET/CT images in MM1.S subcutaneous tumors bearing SCID mice. Tumor volumes ranging from 8.5 to 128.1 mm$^3$ showed efficient tracer uptake. B. $^{89}$Zr-daratumumab-PET/CT image (sagittal and coronal views) of the disseminated MM1.S tumor bearing and control mice. *All mice were injected with 1.11MBq; S.A = 0.37MBq/µg; imaged at 7 days post radiopharmaceutical injection; S=Spleen; Arrows pointing at tumor lesions.

$^{89}$Zr-daratumumab

Courtesy M. Shokeen.
Actinium-225 labeled hu11B6
Summary

• Radioimmunotargeted therapy offers unique opportunity for treating tumors
• Alpha emitters can allow for delivery of higher radiation doses
• Toxicity is mainly marrow based for antibodies
• Smaller molecules may have other organ toxicities
• Theranostic imaging can provide evidence of targeting
  • However, dosimetry is currently a challenge
• Challenges remain:
  • How to achieve Durable control vs limit Toxicity
  • Will tumor control be achievable without significant second organ or marrow toxicity?