Targeted Alpha-Particle Therapy for Acute Myeloid Leukemia

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\[^{225}\text{Ac-lintuzumab}\] is an investigational agent currently in development for use in AML and MDS.
Pathogenesis of Acute Myeloid Leukemia

**Normal Hematopoiesis**

- Erythrocyte
- Megakaryocyte
- Platelets
- CMP
- GMP
- MEP
- Monocyte
- Neutrophil
- Eosinophil
- Basophil
- T-Cell
- B-Cell
- CLP
- HSC

**Leukemogenesis**

1. Lack of Differentiation
   - AML1/ETO
   - PML/RARα
   - MLL rearrangements

2. Increased Proliferation
   - BCR/ABL
   - TEL/PDGFB
   - N-RAS, K-RAS mutants
   - FLT3, c-KIT mutations

Prognostic Factors for AML

Survival by Age\(^1\)

Survival by Karyotype\(^2\)


CD33 Surface Antigen Expression

- **Stem Cell**
- **CFU-GE-MM**
- **BFU-E**
- **CFU-GM**
- **CFU-Meg**
- **Mega**
- **Pro-normoblast**
- **Myeloblast**
- **Pro-myelocyte**
- **Myelocyte**
- **Mono-blast**
- **Mono-cyte**
- **PMN**
- **RBC**
- **Platelets**

**Legend:**
- CD33+ (Blue)
- CD33- (Orange)
Lintuzumab (HuM195, SGN-33)

- Humanized anti-CD33 monoclonal antibody
- Kills target cells by ADCC and fixes complement\(^1\)
- Rapidly targets leukemia cells in patients without immunogenicity\(^2\)
- Has modest activity in relapsed AML\(^3\)
- Can eliminate large leukemic burdens when labeled with the $\beta$-emitters $^{131}$I and $^{90}$Y\(^4,5\)

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\(^3\)Raza A et al. Leuk Lymph 2009; 50:1336-1344.
\(^4\)Burke JM et al. Bone Marrow Transplant. 2003; 32:549-556.
213Bi-Lintuzumab: A 1st Generation α-Emitting Conjugate

### Stable Isotopes

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>225Ac</td>
<td>10.36-37 days</td>
</tr>
<tr>
<td>221Fr</td>
<td>4.9 min</td>
</tr>
<tr>
<td>217At</td>
<td>0.032 sec</td>
</tr>
<tr>
<td>213Bi</td>
<td>46 min</td>
</tr>
</tbody>
</table>

- 10.36-37 MBq/kg delivered in 3-7 fractions over 2-4 days
- Myelosuppression lasted 12-41 days (median, 22 days)
- Transient liver function abnormalities seen in 6 patients
- MTD was not reached
- 14/18 patients had reductions in marrow blasts

## Comparison of $^{131}$I, $^{90}$Y, and $^{213}$Bi Dosimetry for Lintuzumab

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Mean Absorbed Dose (mSv/MBq)</th>
<th>Marrow/Whole Body Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Marrow</td>
<td>Liver</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>2.7</td>
<td>0.8</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>6.8</td>
<td>4.0</td>
</tr>
<tr>
<td>$^{213}$Bi</td>
<td>9.8</td>
<td>5.8</td>
</tr>
</tbody>
</table>

213Bi-Lintuzumab for Cytoreduced Disease

**Rationale and Study Design**

- The short range and high LET make α-particles best suited for treatment of small-volume disease.

- Given the number of CD33 binding sites in AML and achievable specific activity, it is difficult to target adequate numbers of 213Bi atoms to each leukemia cell.

- **Hypothesis**: Cytoreduction with cytarabine should decrease tumor burden by 1-2 logs and increase the ratio of 213Bi atoms to target cells.

**213Bi-Lintuzumab Levels**

- **Level 1**: 18.5 MBq/kg
- **Level 2**: 27.75 MBq/kg
- **Level 3**: 37 MBq/kg
- **Level 4**: 46.25 MBq/kg

**Cytarabine**

- **200 mg/m²/day**

**G-CSF**

**Evaluate for**:
- Toxicity, maximum tolerated dose
- Biodistribution, dosimetry
- Biological effects, remission rate

### $^{213}$Bi-Lintuzumab for Cytoreduced Disease Biodistribution and Clinical Outcomes

#### Results by Disease Status for Doses ≥ 37 MBq/kg

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>No. of Patients</th>
<th>CR</th>
<th>CRp</th>
<th>PR</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated AML, Untreated relapse</td>
<td>18</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>$1^\circ$ refractory, Refractory relapse</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Abbreviations:** CR, complete remission; CRp, CR with incomplete platelet recovery; PR, partial remission.

Actininium-225: An Alpha-Particle Nanogenerator

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
<th>Uses</th>
<th>Stable Isotopes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{225}\text{Ac}$</td>
<td>$\alpha$ 10 days</td>
<td>Short half-life and need for on-site generator limit use of $^{213}\text{Bi}$.</td>
<td></td>
</tr>
<tr>
<td>$^{221}\text{Fr}$</td>
<td>$\alpha$ 4.9 min</td>
<td>$^{225}\text{Ac}$ can be stably conjugated to antibodies using DOTA.</td>
<td></td>
</tr>
<tr>
<td>$^{217}\text{At}$</td>
<td>$\alpha$ 0.032 sec</td>
<td>$^{225}\text{Ac}$-labeled antibodies are 1,000-10,000 times more potent <em>in vitro</em> compared to $^{213}\text{Bi}$ analogs.</td>
<td></td>
</tr>
<tr>
<td>$^{213}\text{Bi}$</td>
<td>$\alpha$ 46 min</td>
<td>Nanocurie doses of $^{225}\text{Ac}$-labeled antibodies prolong survival of mice in xenograft models.</td>
<td></td>
</tr>
</tbody>
</table>

Phase I Trial of $^{225}$Ac-Lintuzumab

- 18 patients with R/R AML received a single dose of 18.5-148 kBq/kg
- DLT was myelosuppression
- No renal toxicity was seen
- MTD was 111 kBq/kg
- Bone marrow blasts were reduced in 10/15 (67%) evaluable patients
- 8 patients (53%) had marrow blast reductions of ≥ 50%
- 3 patients achieved ≤ 5% marrow blasts at doses of 37, 111, and 148 kBq/kg

Pharmacokinetics of $^{225}$Ac-Lintuzumab

- Determined by $\gamma$ counting at energy windows for:
  - $^{221}$Fr (185-250 KeV)
  - $^{213}$Bi (360-480 KeV)

- Two-phase elimination kinetics were seen:
  - Mean plasma $t_{1/2-\alpha} = 1.9$ hrs
  - Mean plasma $t_{1/2-\beta} = 38$ hrs

- Similar to $^{131}$I- and $^{90}$Y- but distinct from $^{213}$Bi-lintuzumab

**Low-Dose Cytarabine Plus $^{225}$Ac-Lintuzumab**

**Objective Responses**

<table>
<thead>
<tr>
<th>Response</th>
<th>Dose Level (kBq/kg/fraction)</th>
<th>Total (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18.5 (n=3)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>37 (n=6)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>CRp</td>
<td>0</td>
<td>1 (17%)</td>
</tr>
<tr>
<td></td>
<td>55.5 (n=3)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>CRI*</td>
<td>0</td>
<td>2 (11%)</td>
</tr>
<tr>
<td></td>
<td>74 (n=6)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Overall</td>
<td>0</td>
<td>5 (28%)</td>
</tr>
<tr>
<td></td>
<td>1 (17%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (67%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (33%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; CRp, CR with incomplete platelet recovery; CRI, CR with incomplete blood count recovery.

All responses seen after Cycle 1.

Jurcic JG et al. SNMMI 2017; abstract 456.
36 patients from initial 2 trials analyzed for response by:

- Age
- Disease characteristics
  - Newly diagnosed vs. relapsed
  - *De novo* vs. secondary AML
  - Genetic risk category
- Disease burden
  - Bone marrow blast percentage
  - Peripheral blood blast count
- Treatment regimen
  - Administered activity
  - Single vs. fractionated dose
  - Monotherapy vs. prior LDAC

Only significant predictor of response was peripheral blood blast count

- Circulating blasts may alter biodistribution leading to decreased delivery of isotope to marrow

Phase II Trial of $^{225}$Ac-Lintuzumab Monotherapy

Study Design and Clinical Outcomes

**Dose (kBq/kg)**

<table>
<thead>
<tr>
<th>Dose (kBq/kg)</th>
<th>Response Rate</th>
<th>Patients with Gr 4 Thrombocytopenia &gt; 6 weeks</th>
<th>Patients with Gr 4 Neutropenia &gt; 6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>74 (n=13)</td>
<td>69%</td>
<td>1 CR, 2 CRp, 6 CRi</td>
<td>46%</td>
</tr>
<tr>
<td>55.5 (n=27)</td>
<td>22%</td>
<td>3 CRp, 3 CRi</td>
<td>30%</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete blood count recovery.

Future Development of $^{225}$Ac-Lintuzumab in AML/MDS

### High-Dose
- Targeted Conditioning
  - Conditioning for HCT in High-Risk MDS
- Combination Therapy
  - Combination with Venetoclax
  - Combination with CLAG-M
  - Combination with 7+3 Induction
- Single-Agent
  - Minimal Residual Disease in AML

**Tailored $^{225}$Ac dose for specific clinical application**
Conclusions

• Early studies with $^{213}$Bi-lintuzumab provided proof-of-principle that systemically administered targeted α-particle therapy is feasible.

• $^{225}$Ac-lintuzumab is active against advanced AML.

• $^{225}$Ac-lintuzumab has produced remissions in older patients with untreated AML as a single agent and in combination with LDAC.

• These studies provide the rationale for use of $^{225}$Ac-lintuzumab in combination with other agents in AML and MDS.
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