Modeling anti-leukemic therapy by patient derived AML xenografts with distinct phenotypes/genotypes

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Abstract

We have recently successfully engrafted leukemic cells, isolated from bone marrows of 3 AML patients with subtypes of M5 (AM7577), M2 (AM8096) and M6 (AM8070), into immunocompromised NOD/SCID mice. The transplanted mice developed AML leukemia with leukemic cells found in bone marrow as in human diseases and also can be found in peripheral organs (e.g. spleen, blood, etc) for some of them (AM7577), seemingly reflective of disease subtypes. Growth of the leukemia cause typical organs (in bone marrow as in human diseases and also can be found in peripheral organs). We have recently successfully engrafted leukemic cells, isolated from different organs.

Table 1. Patient Information

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Subtype</th>
<th>PhenoType</th>
<th>Fusion marker</th>
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<tbody>
<tr>
<td>AM7577</td>
<td>M5</td>
<td>Express: HLA, CD152, CD14, CD571, 38.71</td>
<td>CEBPA Insertion (SNP)</td>
</tr>
<tr>
<td>AM8096</td>
<td>M2</td>
<td>Express: CD13, CD152, CD571, 38, 14, 56, GMA</td>
<td>/</td>
</tr>
<tr>
<td>AM8070</td>
<td>M6</td>
<td>Express: CD13, CD152, CD571, 38, 14, 56, GMA</td>
<td>/</td>
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Figure 1: Genotype analysis of AM7577. Left: IDH2-R140Q; Right: FLT3-LTD.

Figure 2: Histopathology and phenotypic analysis of AM8070. A. Giemsa staining of BM smear; B. Flow cytometry analysis.

Figure 3: Tumor burden growth curve in different organs. A: AM7577; B: AM8096.

Figure 4: The half maximal inhibitory concentration (IC50) curve for AM7577 by treating with A. Ara-C and B. AC-220. Note: The data was done by CellTiter-Glo Luminescent Cell Viability Assay.

Conclusions

1. 3 PDX-AML models have been established;
   a) With typical AML symptoms
   b) Leukemoid load found primarily in BM, as well as in peripheral organs for some models, reflective of patient diseases.
   c) Serially passable in vivo with demonstrated stable genotypes and phenotypes

2. Primary leukemia cells can be used for ex vivo testing.
   a) 2D culture for IC50 (araC, AC220)
   b) 3D (CFC) (araC and AC220)

3. In vivo administration of AraC yield rapid elimination of leukemic load in blood and partial reduction in spleen, but not in BM.
   a) Relieve symptoms and extend life, but without cure
   b) Rapid relapse upon the treatment withdrawal in peripheral

4. AML-7577 with FLT3-LTD respond completely to AC220
   a) High dose treatment lead to cure without relapse long after treatment withdrawal.

5. In summary, these models may serve as useful experimental systems modeling leukemogenesis and pharmacology for AML-7577 with FLT3-LTD respond completely to AC220.