The clinical characteristics, genetic alterations and prognostic significance of De Novo Acute Myeloid Leukemia with hyperleukocytosis

Feng-Ming Tien, Hsin-An Hou, Chien-Yuan Chen, Wen-Chien Chou, Mei-Hsuan Tseng, Ying-Chieh Chiang, Ming-Chih Liu, Chia-Wen Liu, Yuan-Yeh Kuo, Chi-Cheng Li, Chien-Ting Lin, Liang-In Lin, Ming Yao, Shang-Yi Huang, Bor-Sheng Ko, Szu-Chun Hsu, Shang-Ju Wu, Woei Tsay, Jih-Luh Tang, Hwei-Fang Tien

2017.04.16

Division of Hematology, Department of Medicine
National Taiwan University Hospital, Taipei, Taiwan
Introduction

• Acute myeloid leukemia (AML) with hyperleukocytosis (HL) is defined as white blood cell (WBC) counts > 100,000/uL.
• AML with HL was intuitively thought as a unique group with dismal prognosis.
  – Leukostasis
  – Tumor lysis syndrome
  – Disseminated intravascular coagulation
Introduction

• Comprehensive studies regarding the clinical characteristics, genetic alterations in HL patients are limited.

• The role of hematopoietic stem cell transplantation (HSCT) is unclear in HL patients.
Aims of this study

• Analyze our cohort for further understanding the clinical characteristics, genetic alterations and prognostic significance of HL in AML patients.
Patients & Methods

Patients

• 1994~2011, in NTUH
• 755 de novo AML patients
• 101 HL patients, defined as initial white blood cell (WBC) counts >100,000/uL

Methods

• Chromosome analysis
• Mutation analyses by Sanger direct sequencing and next generation sequencing (NGS)
### Baseline characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hyperleukocytosis N=101 (13.4%)</th>
<th>No Hyperleukocytosis N=654 (86.6%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.546</td>
</tr>
<tr>
<td>Male</td>
<td>55</td>
<td>377</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46</td>
<td>277</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>47 (16-90)</td>
<td>54 (15-94)</td>
<td>0.022</td>
</tr>
<tr>
<td>Lab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (/μL)</td>
<td>160860 (103080-627800)</td>
<td>11570 (120-99680)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>7.8 (2.9-12.5)</td>
<td>8.2 (3.2-16.2)</td>
<td>0.179</td>
</tr>
<tr>
<td>Platelet (k/μL)</td>
<td>41 (3-323)</td>
<td>45 (2-1017)</td>
<td>0.680</td>
</tr>
<tr>
<td>Blast (%)</td>
<td>77.6 (0-99)</td>
<td>39 (0-99.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDH</td>
<td>1922 (316-15000)</td>
<td>778 (206-13130)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Induction response</td>
<td></td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>Total CR</td>
<td>69</td>
<td>454</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>44 (63.8%)</td>
<td>355 (78.2%)</td>
<td></td>
</tr>
</tbody>
</table>
**Baseline characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Hyperleukocytosis N=101 (%)</th>
<th>No Hyperleukocytosis N=654 (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>18</td>
<td>1 (5.6)</td>
<td>17 (94.4)</td>
<td>0.493</td>
</tr>
<tr>
<td>M1</td>
<td>165</td>
<td>33 (20)</td>
<td>132 (80)</td>
<td>0.005</td>
</tr>
<tr>
<td>M2</td>
<td>256</td>
<td>20 (7.8)</td>
<td>236 (92.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>M3</td>
<td>64</td>
<td>3 (4.7)</td>
<td>61 (95.3)</td>
<td>0.033</td>
</tr>
<tr>
<td>M4</td>
<td>186</td>
<td>35 (18.8)</td>
<td>151 (81.2)</td>
<td>0.011</td>
</tr>
<tr>
<td>M5</td>
<td>31</td>
<td>10 (32.3)</td>
<td>21 (67.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>M6</td>
<td>27</td>
<td>0 (0)</td>
<td>27 (100)</td>
<td>0.039</td>
</tr>
<tr>
<td>M7</td>
<td>0</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>NA</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>-</td>
</tr>
</tbody>
</table>
Association of HL with cytogenetics

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Total pts</th>
<th>HL (%)</th>
<th>No HL (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>147</td>
<td>9 (9.3)</td>
<td>138 (21.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>t(8;21)</td>
<td>59</td>
<td>0 (0)</td>
<td>59 (9.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>63</td>
<td>3 (3.1)</td>
<td>60 (9.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Inv(16)</td>
<td>26</td>
<td>6 (6.2)</td>
<td>20 (3.1)</td>
<td>0.137</td>
</tr>
<tr>
<td>Intermediate</td>
<td>488</td>
<td>83 (85.6)</td>
<td>405 (63.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Normal</td>
<td>324</td>
<td>61 (62.9)</td>
<td>263 (41.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>-20/20q</td>
<td>6</td>
<td>0 (0)</td>
<td>6 (0.9)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>t(7;11)</td>
<td>9</td>
<td>1 (1.0)</td>
<td>8 (1.3)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>+8</td>
<td>59</td>
<td>1 (1.0)</td>
<td>58 (9.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>+11</td>
<td>14</td>
<td>2 (2.1)</td>
<td>12 (1.9)</td>
<td>0.705</td>
</tr>
<tr>
<td>+13</td>
<td>7</td>
<td>1 (1.0)</td>
<td>6 (0.9)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>+21</td>
<td>24</td>
<td>3 (3.1)</td>
<td>21 (3.3)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>98</td>
<td>5 (5.2)</td>
<td>93 (14.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Complex</td>
<td>76</td>
<td>4 (4.1)</td>
<td>72 (11.3)</td>
<td>0.032</td>
</tr>
<tr>
<td>-5/5q</td>
<td>35</td>
<td>0 (0)</td>
<td>35 (5.5)</td>
<td>0.010</td>
</tr>
<tr>
<td>-7/7q</td>
<td>44</td>
<td>2 (2.1)</td>
<td>42 (6.6)</td>
<td>0.082</td>
</tr>
<tr>
<td>Unknown</td>
<td>24</td>
<td>5</td>
<td>19</td>
<td>-</td>
</tr>
</tbody>
</table>
# Association of HL with genetic alterations

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Exam. No</th>
<th>Patient with gene mutations (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>HL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FLT3-ITD</strong></td>
<td>662</td>
<td>144</td>
<td>35 (38.9)</td>
</tr>
<tr>
<td><strong>NPM1</strong></td>
<td>751</td>
<td>147</td>
<td>29 (28.7)</td>
</tr>
<tr>
<td><strong>CEBPA_sm</strong></td>
<td>750</td>
<td>98</td>
<td>26 (26.0)</td>
</tr>
<tr>
<td><strong>CEBPA_dm</strong></td>
<td>750</td>
<td>65</td>
<td>15 (14.9)</td>
</tr>
<tr>
<td><strong>NRAS</strong></td>
<td>481</td>
<td>82</td>
<td>14 (20.9)</td>
</tr>
<tr>
<td><strong>DNMT3A</strong></td>
<td>748</td>
<td>120</td>
<td>20 (19.8)</td>
</tr>
<tr>
<td><strong>TET2</strong></td>
<td>732</td>
<td>82</td>
<td>19 (19.4)</td>
</tr>
<tr>
<td><strong>ASXL1</strong></td>
<td>753</td>
<td>99</td>
<td>17 (17.0)</td>
</tr>
<tr>
<td><strong>IDH2</strong></td>
<td>753</td>
<td>87</td>
<td>15 (14.9)</td>
</tr>
<tr>
<td><strong>FLT3-TKD</strong></td>
<td>752</td>
<td>73</td>
<td>14 (13.9)</td>
</tr>
<tr>
<td><strong>GATA2</strong></td>
<td>755</td>
<td>44</td>
<td>9 (8.9)</td>
</tr>
<tr>
<td><strong>WT1</strong></td>
<td>750</td>
<td>52</td>
<td>8 (8.0)</td>
</tr>
<tr>
<td><strong>RUNX1</strong></td>
<td>746</td>
<td>96</td>
<td>8 (8.0)</td>
</tr>
<tr>
<td><strong>IDH1</strong></td>
<td>752</td>
<td>44</td>
<td>6 (5.9)</td>
</tr>
<tr>
<td><strong>MLL/PTD</strong></td>
<td>696</td>
<td>36</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td><strong>KIT</strong></td>
<td>753</td>
<td>33</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>748</td>
<td>54</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td><strong>KRAS</strong></td>
<td>480</td>
<td>19</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
HL predicts shorter OS and DFS

- Median OS: HL vs. No HL (24 months vs. not reached)
- Median DFS: HL vs. No HL (6.5 vs. 11.8 months)
HL is an independent poor prognosis factor

<table>
<thead>
<tr>
<th>Variables</th>
<th>DFS Uni-P Value</th>
<th>DFS Multi-P Value</th>
<th>DFS RR (CI)</th>
<th>OS Uni-P Value</th>
<th>OS Multi-P Value</th>
<th>OS RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.005</td>
<td>0.010</td>
<td>1.44 (1.12-1.85)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>2.17 (1.55-3.04)</td>
</tr>
<tr>
<td>WBC&gt;100K</td>
<td>0.003</td>
<td>0.010</td>
<td>1.62 (1.15-2.28)</td>
<td>0.044</td>
<td>0.004</td>
<td>1.99 (1.24-3.18)</td>
</tr>
<tr>
<td>Karyotype</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>2.27 (1.50-3.44)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>3.48 (2.16-5.60)</td>
</tr>
<tr>
<td>biCEBPA</td>
<td>0.012</td>
<td>0.182</td>
<td>0.74 (0.48-1.15)</td>
<td>0.004</td>
<td>0.118</td>
<td>0.58 (0.29-1.15)</td>
</tr>
<tr>
<td>MLL/PTD</td>
<td>0.001</td>
<td>0.013</td>
<td>1.88 (1.14-3.09)</td>
<td>0.065</td>
<td>0.170</td>
<td>1.67 (0.80-3.48)</td>
</tr>
<tr>
<td>ASXL1</td>
<td>0.082</td>
<td>0.641</td>
<td>1.12 (0.72-1.74)</td>
<td>0.032</td>
<td>0.582</td>
<td>1.18 (0.66-2.09)</td>
</tr>
<tr>
<td>IDH1</td>
<td>0.409</td>
<td></td>
<td></td>
<td>0.359</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH2</td>
<td>0.726</td>
<td></td>
<td></td>
<td>0.376</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TET2</td>
<td>0.462</td>
<td></td>
<td></td>
<td>0.083</td>
<td>0.723</td>
<td>1.10 (0.64-1.89)</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>0.001</td>
<td>0.003</td>
<td>1.67 (1.18-2.35)</td>
<td>0.002</td>
<td>0.076</td>
<td>1.48 (0.96-2.29)</td>
</tr>
<tr>
<td>NPM1+/FLT3-</td>
<td>0.023</td>
<td>0.003</td>
<td>0.48 (0.29-0.73)</td>
<td>0.163</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRAS</td>
<td>0.918</td>
<td></td>
<td></td>
<td>0.863</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>0.110</td>
<td></td>
<td></td>
<td>0.259</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTPN11</td>
<td>0.459</td>
<td></td>
<td></td>
<td>0.202</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIT</td>
<td>0.245</td>
<td></td>
<td></td>
<td>0.154</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P53</td>
<td>&lt;0.0001</td>
<td>0.119</td>
<td>1.57 (0.89-2.77)</td>
<td>&lt;0.0001</td>
<td>0.004</td>
<td>2.35 (1.32-4.20)</td>
</tr>
<tr>
<td>WT1</td>
<td>0.001</td>
<td>0.003</td>
<td>1.89 (1.29-2.78)</td>
<td>0.006</td>
<td>0.001</td>
<td>2.33 (1.39-3.91)</td>
</tr>
<tr>
<td>GATA2</td>
<td>0.176</td>
<td></td>
<td></td>
<td>0.130</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUNX1</td>
<td>0.001</td>
<td>0.016</td>
<td>1.65 (1.11-2.46)</td>
<td>0.001</td>
<td>0.191</td>
<td>1.41 (0.84-2.38)</td>
</tr>
</tbody>
</table>
HSCT ameliorates the poor survival impact of HL

No transplant (n=350)
- Median OS: HL vs. No HL (10.7 vs. 40.5 months)

Transplant (n=174)
- Median OS: HL vs. No HL (39.7 vs. 55.2 months)
Discussion

• 5% to 20% of AML patients presented with HL.
• HL
  – Associated with FAB M4, M5
  – More FLT3-ITD (45%), and NPM1 mutations (44%)
• AML with HL had poor prognosis
  – Median overall survival (OS) was 8.8 months
  – Even after HSCT, relapse rate is higher than non-HL (30% vs. 22%, P=0.013)
Conclusion

• The HL patients represent 13.4% of our AML cohort.

• HL patients
  – Younger age
  – Associated with FAB M1, M4, M5
  – Associated with intermediate-risk cytogenetics
  – More \textit{FLT3-ITD} (38.9%), \textit{NPM1} (28.7%), \textit{CEBPA} (26%), and \textit{TET2} (19.4%) mutations
Conclusion

• HL is associated with lower CR rate.
• HL is an independent poor prognosis factor on OS and DFS irrespective of cytogenetics change or mutation status.
• HL patients may potentially benefit from HSCT.
Acknowledgments

**Lab colleagues**
- Hwei-Fang Tien, MD, PhD
- Wen-Chien Chou, MD, PhD
- Hsin-An Hou, MD, PhD
- Chien-Chin Lin, MD
- Mei-Hsuan Tseng
- Chi-Fei Huang

**Statistical Analysis**

**Chromosomal analysis**
- Ming-Chih Liu

**Hematologists**
- Yao-Chang Chen, MD
- Woei Tsai, MD, PhD
- Jih-Luh Tang, MD, PhD
- Ming Yao, MD
- Chi-Cheng Li, MD
- Shang-Yi Huang, MD, PhD
- Bor-Sheng Ko, MD, PhD
- Szu-Chun Hsu, MD
- Chien-Yuan Chen, MD, PhD
- Shang-Ju Wu, MD, PhD
- Chien-Ting Lin, MD

*All patients that participated this study*