Clinical Implications of Clonal Hematopoiesis

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Disclosures

• None
Myeloid precursor lesions added to WHO 2022, CHIP and CCUS formally defined
Clonal Hematopoiesis of Indeterminate Potential

• (WHO) Classification defined CHIP as the presence of a somatic mutation associated with myeloid neoplasia detected in the peripheral blood or bone marrow with a VAF ≥ 2% in the absence of definitive morphologic evidence of a hematologic disorder
  • Dominant mutations: TP53, TET2, DNMT3A, ASXL1, JAK2

• Prevalence of CH increases with age – 10%-15% of 60 to 70 years of age
  • With a VAF of ≥0.01% the prevalence of CH to be nearly ubiquitous in persons >50 years of age

• CH is 5 to 10 times higher in patients who have received cytotoxic chemotherapy or ionizing radiation

• CHIP is associated with decreased overall survival, increased risk for a hematologic malignancy, and cardiovascular complications, compared with age-matched individuals without CHIP
  • Increase mortality occurred in those 70 + years old, not younger individuals
  • Excessive mortality is driven by cardiovascular events rather than hematologic neoplasms

CHIP and Hematologic Malignancies

• CHIP is associated with an increased risk of transformation to myeloid neoplasms

• Only a small fractions of individuals with CHIP will develop hematologic malignancies
  • Risk of evolution to AML is estimate at 0.5% to 1% per year
  • Prevalence in 70-year-olds is 100-fold greater than prevalence or MDS or leukemia

• Risk factors for developing myeloid malignancies
  • Age 65 years or greater
  • High-risk mutations (SF3B1, SRSF2, ZRSR2, JAK2, TP53, RUNX1, FLT3, IDH1, or IDH2).
  • VAF ≥20 percent
  • ≥2 distinct mutations
  • Cytopenias
  • RBC indices (RDW ≥15 percent or MCV >100 fL)

Bejar R. CHIP, ICUS, CCUS and other 4 letter words. Leukemia 2017;31:1869
<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single DNMT3A</td>
<td>present</td>
<td>absent</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>High Risk Mutation</td>
<td>-</td>
<td>absent</td>
<td>-</td>
<td>-</td>
<td>present</td>
</tr>
<tr>
<td>Mutation Number</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>≥ 2</td>
<td>-</td>
</tr>
<tr>
<td>Variant Allele Fraction</td>
<td>-</td>
<td>&lt; 0.2</td>
<td>-</td>
<td>&gt; 0.2</td>
<td>-</td>
</tr>
<tr>
<td>Red Cell Distribution Width</td>
<td>-</td>
<td>&lt; 15</td>
<td>-</td>
<td>-</td>
<td>≥ 15</td>
</tr>
<tr>
<td>Mean Corpuscular Volume</td>
<td>-</td>
<td>&lt; 100</td>
<td>-</td>
<td>-</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>-</td>
<td>CHIP</td>
<td>CCUS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>-</td>
<td>&lt; 65y</td>
<td>≥ 65y</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk</th>
<th>% of patients</th>
<th>% 10yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>88.4%</td>
<td>93.7%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10.5%</td>
<td>84.0%</td>
</tr>
<tr>
<td>High</td>
<td>1.1%</td>
<td>51.2%</td>
</tr>
</tbody>
</table>

## Risk-Stratification Model to Predict Progression of MGUS to MM or Related Disorders

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Relative Risk</th>
<th>Absolute Risk of Progression (20 Years), %</th>
<th>Absolute Risk of Progression (20 Years), Accounting for Death as a Competing Risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low – no risk factors present</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>(39% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-intermediate – 1 risk factor</td>
<td>5.4</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>present (37% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-intermediate – 2 risk factors</td>
<td>10.1</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>present (20% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High – all 3 risk factors present</td>
<td>20.8</td>
<td>58</td>
<td>27</td>
</tr>
<tr>
<td>(4% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### MGUS
- Prevalence in general population
  - >50year 3.4%, >70year 5.3%, >80year 7.5%
- Mean age of detection 70 years
- Only 1% of patients go on to develop myeloma in a year
- Lifetime risk of progression ~10%
- Virtually all malignant plasma cell dyscrasias are preceded by MGUS
- Median survival of individuals only slightly shorter than that of age-matched controls

### Monitoring
- Screening is not recommended
- No prospective studies to proven the benefits of monitoring
- Observational studies of population-based cohorts with MGUS
  - associated with improved survival and less morbidity in those who progress to myeloma
  - Unclear whether this benefit was due to earlier detection and initiation of treatment or lead-time bias.

Adapted from Blood. 2005;106:812-817
MDS overlap disorders and diagnostic boundaries

Tiffany N. Tanaka, Rafael Bejar, MDS overlap disorders and diagnostic boundaries, Blood, 2019,
Adjusted HR for incident CHD among Jackson Heart Study & FUSION participants


Clinical Interpretation – The Next Bottleneck

A major goal of cancer genomics is identifying “actionable” mutations that drive a tumor and can be targeted with available therapy **BUT**…

“Then you have a 5-inch-thick set of papers on your desk for the bioinformatics. That’s where the cost is.”

(Gail Vance, Director of Diagnostic Genomics, Indiana U. School of Medicine)

- **2000+ MDx tests**
- **NGS data (100s of genes to 6MB genome)**
- **2.8M+ peer-reviewed papers on cancer**
- **900+ therapeutics in clinical development**
- **3500+ novel treatment approaches**
- **10,000+ ongoing clinical trials**

**New technologies**

- Ever-increasing amount of data growing complexity for physicians & patients to process
  - NGS data • MDx & pathology results • Growing body of cancer & biomarker literature • New targeted therapies • Combination therapy • Clinical Trials
- Physicians will need greater information on the appropriate integration of molecular testing into treatment decision making.
Thanks

Hello, here is my tumor sequence