Microarray-based classifiers and prognosis models identify subgroups with distinct clinical outcomes and high risk of AML transformation of myelodysplastic syndrome


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Overview

• Myelodysplastic syndromes: definition and classification

• Background

• Methods

• Results

• Discussion
MyeloDysplastic Syndromes (MDS)

• MDS= clonal haematopoietic stem cell diseases characterized by
  – Cytopenia(s)
  – Dysplasia in myeloid cell lines
  – Ineffective haematopoiesis
  – Increased risk of Acute Myeloid Leukemia (AML)

• Diagnostic criteria:
  – Blast %
  – Dysplasia
  – Presence of ring sideroblasts
Myelodysplastic syndromes

• WHO classification of MDS (1997)
  – Refractory anaemia
  – Refractory anaemia with ring sideroblasts
  – Refractory anaemia with excess blasts (RAEB)
  – Refractory cytopenia with multilineage dysplasia
  – 5q- syndrome
  – Unclassifiable MDS
  – Chronic myelomonocytic leukemia (CMML)

• International Prognostic Scoring System (IPSS) for MDS

<table>
<thead>
<tr>
<th>Score/Prognostic variables</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>% bone marrow blasts</td>
<td>&lt;5%</td>
<td>5-10%</td>
<td>11-19%</td>
<td>20-30%</td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0-1</td>
<td>2-3</td>
<td></td>
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</table>
Background (1)

• **Original design:**
  – Standardized
  – Objective
  – Molecularly based (GEP)

• **Target:**
  – 16 subclasses of acute or chronic leukemia
  – MDS

Diagnostic classification model
Background (2)

• Results
  – 95% accuracy for leukemia categories
  – 50% accuracy for MDS \[\Rightarrow\text{unexpected & disappointing}\]

• New objective:
  Development of a “time-to-AML transformation” risk score
**Methods**

*Flow chart showing the relationship of datasets used in the study.*

- **174 MDS cases collected as part of the MILE study and classification analysis performed with Diagnostic Classifier (DC) model.**
- **164 samples (cohort N164), confirmed as MDS by external blinded expert review. Note: 10 samples re-assigned to other diagnoses.**
- **25 CMML samples excluded based on WHO criteria.**
- **139 validated MDS samples excluding CMML (cohort N139).**
- **110 validated MDS samples with outcome data (cohort N110).**
- **Exclusion of CMML.**
- **Exclusion of patients without outcome data.**

Results

*Kaplan-Meier curves grouped by Prognostic classification model score*

**Overall survival**

<table>
<thead>
<tr>
<th>Multicovariate hazard ratios</th>
<th>Overall survival</th>
<th>Time to AML transformation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>$P$</td>
<td>Hazard ratio</td>
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<tr>
<td>IPSS score</td>
<td>.584</td>
<td>1.10</td>
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<tr>
<td>DC model</td>
<td>.628</td>
<td>1.11</td>
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<td>PC model</td>
<td>.009*</td>
<td>1.60</td>
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</table>

*p<0.05*
Discussion

• Significant correlation with time to AML transformation
  => Prognostic algorithm non-observer dependent

• Limits
  – Retrospective study
  – Redefinition of objectives during the study
  – Validated IPSS does NOT stand out as prognostic factor
Take home message

• New approach on diagnostic & prognostic scoring based on GEP instead of cytomorphology

• GEP appears to be a promising objective classification method

• Prospective study required to validate these results
Bibliography


• “Classification of Tumors of Haematopoietic and Lymphoid Tissues”, WHO publication