Update on MDS Risk Stratification

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Outline

• Traditional MDS prognostic scores (IPSS, IPSS-R, WPSS):
  ➔ Advantages
  ➔ Limitations

• New prognostic scores:
  ➔ Comorbidity
  ➔ Molecular
Myelodysplastic syndromes: 2018 update on diagnosis, risk-stratification and management

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Abstract
Disease overview: The myelodysplastic syndromes (MDS) are a very heterogeneous group of myeloid disorders characterized by peripheral blood cytopenias and increased risk of transformation to acute myelogenous leukemia (AML). MDS occurs more frequently in older males and in
Why risk stratify?

• The prognosis of patients with MDS is very heterogeneous
Background

• The natural history of patients with MDS is variable
• Several patient and disease related characteristics have been shown to be prognostic.
• Prognostic systems have also been developed
• Valuable in guiding treatment decisions
  • in particular helping to outline high risk patients who may benefit from transplant
Background

• The two most commonly used scoring systems are:
  • International Prognostic Scoring System (IPSS)
  • The revised International Prognostic Scoring System (IPSS-R)
IPSS vs IPSS-R

**IPSS:**
- Survival data of 816 patients with de novo MDS
- Based upon the French American British (FAB) classification system
- Treated in general with supportive care only

**WHO criteria**
- Decreased blast threshold for AML from 30% to 20%

**IPSS-R:**
- Data from 2902 patients with de novo MDS
- Diagnosed using the FAB or WHO classifications
- Validated in an independent cohort of 1632 patients
- Treated with supportive care only

1997 | 2008 | 2012
International Prognostic Scoring System Revised (IPSS-R).

Calculate risk score

Cytogenetic risk group:
- very good
- good
- intermediate
- poor
- very poor

Bone marrow blast %:
- ≤ 2%
- > 2% - ≤ 5%
- 5% - 10%
- > 10%

Hemoglobin (g/dL):
- ≥ 10
- 8 - < 10
- < 8

Platelet count (x 10^9/L):
- ≥ 100
- 50 - < 100
- < 50

Absolute neutrophil count (x 10^9/L):
- ≥ 0.8
- < 0.8

Assign IPSS-R risk group

<table>
<thead>
<tr>
<th>Total score</th>
<th>% of patients</th>
<th>Median survival, years</th>
<th>Time to 25% with AML, years</th>
<th>IPSS-R risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5</td>
<td>15%</td>
<td>8.8</td>
<td>not reached</td>
<td>very low</td>
</tr>
<tr>
<td>0.5 - 1.5</td>
<td>35%</td>
<td>5.3</td>
<td>19.8</td>
<td>low</td>
</tr>
<tr>
<td>0 - 0.5</td>
<td>50%</td>
<td>3.3</td>
<td>3.2</td>
<td>intermediate</td>
</tr>
<tr>
<td>&lt; 0.5</td>
<td>13%</td>
<td>1.6</td>
<td>1.4</td>
<td>high</td>
</tr>
</tbody>
</table>

Graphs showing overall survival and time to AML evolution.
IPSS

• In place since 1997.
• Highly reproducible and very simple to use.
• Has several limitations.
  • it is not a precise predictor in pts with lower risk
  • relatively little weight to cytogenetics.
IPSS-R

• IPSS-R provides a more discriminatory prognostic power
  • a larger number of cytogenetic abnormalities
  • a lower cut off for absolute neutrophil count
• IPSS-R is the standard risk assessment tool in MDS
• Limitations exist
  • no drug therapy has been approved using IPSS-R yet
Should IPSS-R be a target for improvement?

• If you improve IPSS-R ⇒ better outcomes??
Improving Revised International Prognostic Scoring System (IPSS–R) Pre-Allogeneic Stem Cell Transplant Does Not Translate into Better Post-Transplant Outcomes for Patients with Myelodysplastic Syndromes


Blood 2016 128:4662,
Methods

• IPSS-R was calculated at MDS diagnosis and then re-calculated at the time of transplant.
• Outcomes of pts who had improvement in IPSS-R were then compared to those with no improvement.
• Example:

<table>
<thead>
<tr>
<th>Very low</th>
<th>Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Unchanged</td>
</tr>
<tr>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>Worse</td>
</tr>
</tbody>
</table>
Alzahrani et al. 2016
Alzahrani et al. BBMT. 2018

Overall Survival based on blast % at transplant

P = 0.004
When to best use scoring systems?

• Most scoring systems assess prognosis **at the time of diagnosis**.
  ▪ assuming **stable** predictability over the disease course.
Limitations

• Moderate loss of prognostic power over time.

Time-dependent changes in mortality and transformation risk in MDS

Patient characteristics

• 7212 untreated primary MDS pts
• Pts were diagnosed by FAB and/or WHO classifications.
• Cytogenetic were classified by original IPSS and by the IPSS-R.
Results

• Changes in the subgroup-specific hazards over time:

Figure 1. Survival of IPSS-R-classified patient subgroups using smoothed hazard plots and corresponding Kaplan-Meier curves (representative example). (A)
Attenuation of hazards over time was evident for all scoring systems. After approximately 3.5 years, hazards in the separate risk groups become similar. Scores applied to lower-risk patients remain more stable over time.
Low risk patients

- It has become apparent that the natural history of patients with lower risk disease is very heterogeneous.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfavorable cytogenetics</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>2</td>
</tr>
<tr>
<td>Hemoglobin &lt; 10 g/dL</td>
<td>1</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
</tr>
<tr>
<td>&lt; 50 × 10⁹/L</td>
<td>2</td>
</tr>
<tr>
<td>50–200 × 10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>Bone Marrow Blasts ≥ 4%</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Median Survival</th>
<th>4-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NR</td>
<td>78</td>
</tr>
<tr>
<td>1</td>
<td>83</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>51</td>
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<tr>
<td>3</td>
<td>36</td>
<td>40</td>
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<td>4</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Lower risk MDS pts

Figure 2  Risk model for the whole group of patients.
The WHO Prognostic Scoring System

• WPSS was developed using data from 426 pts with de novo MDS
• Designed for pts diagnosed by WHO classification.
• Incorporates information on RBC transfusion need
• Advantage over the IPSS:
  • able to be used at any time during the disease course and
  • has prognostic value post transplant
Molecular IPSS

• New molecular IPSS system is expected soon.
• Several studies confirm the added value of mutational data in risk stratification:
Mayo clinic experience

• Mayo clinic attempted to reproduce the IPSS-R cytogenetic model in 783 pts with primary MDS
  • was unable to delineate the five cytogenetic categories.
• Instead, identified monosomal karyotype (MK) as the most important marker of inferior survival
  • since validated by other investigators.
Mayo clinic cytogenetic risk groups

- High-risk: MK
- Low-risk:
  - NK
  - **single** abnormalities of -Y, 11q-, 20q-, 12p-, 11q-, 5q-
  - **two** abnormalities including 5q-
- Intermediate-risk: **all other** abnormalities.
• Mutations and prognosis in myelodysplastic syndromes: karyotype-adjusted analysis of targeted sequencing in 300 consecutive cases and development of a genetic risk model

• Naseema Gangat,1 Mythri Mudireddy,1 Terra L. Lasho,1 Christy M. Finke,1 Maura Nicolosi,1 Natasha Szuber,1 Mrinal M. Patnaik,1 Animesh Pardanani,1 Curtis A. Hanson,2 Rhett P. Ketterling,3 Ayalew Tefferi.1

• Divisions of 1Hematology, 2Hematopathology and 3Laboratory Genetics and Genomics, Departments of Internal and Laboratory Medicine, Mayo Clinic, Rochester, MN, USA
• Univariate analysis in 300 pts with primary MDS.
• Identified:
  • Unfavorable: \textit{TP53, RUNX1, U2AF1, ASXL1, EZH2} and \textit{SRSF2} mutations as
  • Favorable: \textit{SF3B1}
• Multivariable analysis adjusted for age and MK.
• A simple risk model that is based on:
  • age
  • karyotype
  • mutations
Figure 1: Survival data on 200 patients with primary myelodysplastic syndromes stratified by cytogenetic risk groups according to:
(a) The revised international prognostic scoring system (IPSS-R) cytogenetic categories
(b) monosomal karyotype (Mk) modified IPSS
(c) a simplified three-tiered cytogenetic risk stratification (Mayo cytogenetic risk model)
Global MDACC

- Both the IPSS and IPSS-R excluded patients with CMML or t-MDS.
- To overcome these limitations, the global MDACC model was developed.
  - It allows evaluation at any time during the course of the disease.
Kantarjian et al. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System.


<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS $\geq$ 2</td>
<td>2</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>60–64</td>
<td>1</td>
</tr>
<tr>
<td>$&gt;$ 64</td>
<td>2</td>
</tr>
<tr>
<td>Platelets $\times 10^9$/L</td>
<td></td>
</tr>
<tr>
<td>$&lt;$ 30</td>
<td>3</td>
</tr>
<tr>
<td>30–49</td>
<td>2</td>
</tr>
<tr>
<td>50–199</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin $&lt;$ 12 g/dL</td>
<td>2</td>
</tr>
<tr>
<td>BM blast %</td>
<td></td>
</tr>
<tr>
<td>5 to 10</td>
<td>1</td>
</tr>
<tr>
<td>11 to 19</td>
<td>2</td>
</tr>
<tr>
<td>WBC $&gt; 20 \times 10^9$/L</td>
<td>2</td>
</tr>
<tr>
<td>Alteration of chromosome 7 or $\geq$ 3 alterations</td>
<td>3</td>
</tr>
<tr>
<td>Prior transfusion</td>
<td>1</td>
</tr>
</tbody>
</table>
Comorbidity score

• MDS occurs in older patients ➔ comorbidities.
• None of the systems discussed included impact of comorbidity.
• There is a comorbidity score known as ACE-27.
• Presence of comorbidity had a significant independent impact on survival.
  • Naqvi K et al. Association of comorbidities with overall survival in myelodysplastic syndrome: development of a prognostic model. JCO.2011;29(16):2240–2246.
Conclusion

• Multiple risk scores present for MDS
• Important to know the limitation
• Lower risk IPSS pts are heterogeneous
• Future:
  • Dynamic scores
  • Molecular
Questions?

Thanks