Prognostic Scoring Systems for Therapeutic Decision Making in MDS

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DISCLOSURE

I have no relevant financial relationships to disclose.
MDSs: A Spectrum of Diseases

- **Clinical heterogeneity** \((0.8-8.0 \text{ yr median OS})\)
  - Marrow morphology: % blasts, dysplasia, fibrosis, ring sideroblasts, cellularity
  - HPC/Blast Immunophenotype/Flow cytometry
  - Prognostic classifications—IPSS, WPSS, IPSS-R
  - Therapeutic options/responses

- **Biologic heterogeneity**—marrow stems & stroma
  - Cytogenetic, Molecular
  - Immunologic, Phagocytic, Aberrant Cytokines
Prognostic Features in MDS

• Clinical
  – CBC, marrow blasts, cytogenetics
  – Age, PS, ferritin, LDH, β2M, marrow fibrosis
  – Flow cytometry
    • lineage infidelity, aberrant antigen expression
  – Treatment/Response

• Molecular
  – Specific mutations
  – Number of mutations
Primary MDS

- Normal karyotype: 40%
- Balanced abnormalities: 30%
- Abnormal chromosome 5 and/or 7: 22%
- Other unbalanced abnormalities: 8%

Olney & LeBeau, 2006

t-MDS

- Abnormal chromosome 5 and/or 7: 75%
- Other unbalanced abnormalities: 12%
- Normal karyotype: 9%
- Balanced abnormalities: 4%
**INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS) FOR MYELODYSPLASTIC SYNDROMES**

Survival and AML Evolution

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Marrow Blasts (%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Low</th>
<th>INT-1</th>
<th>INT-2</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>0</td>
<td>0.5 - 1.0</td>
<td>1.5 - 2.0</td>
<td>≥ 2.5</td>
</tr>
</tbody>
</table>

Cytogenetics Abnormalities in MDS

- Y: 17 (2%)
- del(5q): 48 (6%)
- Normal: 489 (60%)
- del(20q): 16 (2%)
- Misc. single: 74 (9%)
- +8: 38 (5%)
- Double: 29 (3%)
- Misc. double: 14 (2%)
- Chrom 7 abn: 10 (1%)
- Misc. complex: 15 (2%)
- Complex: 66 (8%)

International MDS Workshop
Del (5q) MDS: Prognostic Impact of Additional Cytogenetic Abnormalities
Mallo et al, Leukemia 2010
International MDS Risk Classification

Survival

- Low: 267 pts
- Int-1: 314 pts
- Int-2: 179 pts
- High: 56 pts

Years: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Percent: 100 90 80 70 60 50 40 30 20 10 0

AML Evolution

- Low: 235 pts
- Int-1: 295 pts
- Int-2: 171 pts
- High: 58 pts

Years: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Percent: 100 90 80 70 60 50 40 30 20 10 0

International MDS Workshop
Blood 89: 2079, 1997
MDS Classifications

- 1997  IPSS/IMRAW (FAB): 816 pts/7 DBs
- 2001  WHO classification
- 2005  WPSS: 1165 pts/3 DBs

- 2001-2011  **New features** described as possible additional prognostic factors

- 2012 New cytogenetic classification: 2900 pts/4 DBs
- 2012 IWG-PM Refined consensus system (IPSS-R)
  - Primary Untreated MDS
  - 7012 pts/11 countries
    - MDS Fndn, Research support: Celgene, Amgen
IWG-PM/IPSS-R
11 Countries: 7012 patients

- Austria
- Brazil
- Czech Rep
- France
- Germany
- Italy
- Japan
- Netherlands
- Scotland
- Spain
- USA

*Blood 120:2454, 2012
(under the aegis of The MDS Foundation)*
Prognostic Classification Systems for MDS and CMML

<table>
<thead>
<tr>
<th></th>
<th>Blasts</th>
<th>Cyto</th>
<th>Hb</th>
<th>Plts</th>
<th>ANC</th>
<th>Age</th>
<th>RBC txns</th>
<th>PS</th>
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<tbody>
<tr>
<td>IPSS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>WPSS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>MDA-L</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>FPSS</td>
<td>+(PB)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>CPSS</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>IPSS-R*</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

*Plus other variables: LDH, ferritin, β2-microglobulin, fibrosis
Cytogenetic Prognostic Groups: IPSS-R, Blood 9/12, n=7012

- **Very Good**: -Y, 11q-
- **Good**: Nl, 20q-, 5q-, 12p-
- **Int**: +8, +19, +21, i(17q), 7q-, 1 or 2 other clones
- **Poor**: -7, double w/ 7q-, der(3), Complex(3abn)
- **Very Poor**: Complex >3
### IPSS-R for MDS: Prognostic Score Values

*IWG-PM, Blood 120:2454, 2012*

<table>
<thead>
<tr>
<th>Cyto</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>VG</td>
<td>Good</td>
<td>Int</td>
<td>Poor</td>
<td>VP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blast %</td>
<td>≤2</td>
<td>&gt;2-&lt;5</td>
<td>5-10</td>
<td>&gt;10</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hb</th>
<th>≥10</th>
<th>8-&lt;10</th>
<th>&lt;8</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Plts</th>
<th>≥100</th>
<th>50-</th>
<th>&lt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;100</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANC</th>
<th>&gt;0.8</th>
<th>≤0.8</th>
</tr>
</thead>
</table>

[http://advanced.ipss-r.com](http://advanced.ipss-r.com)
IPSS-R Categories: Clinical Outcomes

*IWG-PM, Blood 9/12, n=7012*

**Risk Score; Median OS**

- **Very Low**: $\leq 1.5$; 8.8yr
- **Low**: 1.5-3; 5.3yr
- **Int**: 3-4.5; 3 yr
- **High**: 4.5-6; 1.6yr
- **Very High**: $\geq 6$; 0.8yr
IPSS-R Prognostic Risk-Based Categories

Survival

Freedom from AML Evolution

IWG-PM, Blood 9/2012; http://advanced.ipss-r.com
## IPSS-R: Additive Prognostic Variables

<table>
<thead>
<tr>
<th></th>
<th>Total cases</th>
<th>Survival</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>100%</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>PS/ECOG</td>
<td>36%</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Ferritin</td>
<td>43%</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>19%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LDH</td>
<td>59%</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>β2M</td>
<td>15%</td>
<td>(+++)</td>
<td>-</td>
</tr>
</tbody>
</table>
IPSS-R for Untreated MDS: Advances Beyond the IPSS

- Refined cytogenetic subgroups (16 vs 7) & prognostic categories (5 vs 3)
- Depth of cytopenias analyzed
- ↑ Predictive power for survival & AML (5 vs 4)
  - Shift ~20% lower and higher risk into Intermediate group
- Additional predictive features for survival
  - AGE, PS, ferritin, LDH
- Clinical management risk categories
  - Lower (Very Low/Low), Intermediate, Higher (High/Very High)
MDS: Risk-Based Clinical Outcomes
Voso et al, J Clin Oncol 2013, MDS Gruppo Romano, n=380

IPSS

WPSS

IPSS-R

Survival, p<.001

LFS, p<.001
Risk Scoring Systems: Prognostic Power Δ/Time
Pfeilstocker, Tuechler et al, for the IWG-PM, Proc ASH ’13 #1544

• Untreated MDS patients, IWG-PM DB, n=7212
• Some loss of prognostic power occurs for all systems over time from diagnosis
  – IPSS-RA < IPSS-R ≅ WPSS < IPSS
  – Retention: Lower > Int >> Higher risk patients
  – IPSS-R Intermediate:
    Prognosis retained for LFS, ➔ High risk for OS
IPSS-R: Response to ESAs
Santini et al, Proc ASH ‘13 #2761, n=456 IPSS Low/Int1

- Serum epo <500, Hb≤10, RBC Txn dep’t 29%
- IPSS-R Erythroid responses (HI-E) 61% (IWG 2006)
  - 15% Very Low 85%
  - 61% Low 68%
  - 19% Intermediate 48%
  - 4% High 31%
- New HI-E score (0-4):
  - IPSS-R$_{0-3}$, serum epo >200, ferritin >350
  - HI-E: 85, 64, 40, 20%
Clinical Outcomes of Treated MDS Patients Categorized by IPSS-R

Sekeres, Ades, Tuechler et al for the IWG-PM, n=882; Int’l MDS Symp’m 2013
MDS: Post-Allogeneic HSC Transplant Outcome: Relation to Pre-Transplant IPSS-R Risk Category

GITMO study, n=519, Della Porta et al, Proc ASH 2013, #2765
HSCT in MDS: Adjusted Probability of Survival

Overall P-value=0.005 (2 df)
8/8 MUD vs. MRD= 1.24 (0.98-1.56)
7/8 MUD vs. MRD= 1.62 (1.21-2.17)
7/8 MUD vs. 8/8 MUD=1.30 (1.01-1.68)

Saber et al, CIBMTR, ASH ’12, #355
Other Prognostic Factors for Relapse
Saber et al, CIBMTR, ASH ‘12, #355, n=699 HSCTs

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relapse Risk (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease status at HCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (≤5% BM blasts)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>1.97 (1.37-2.84)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>IPSS at diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-risk</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Int-1</td>
<td>2.28 (1.07-4.81)</td>
<td>0.03</td>
</tr>
<tr>
<td>Int-2</td>
<td>1.88 (0.86-4.09)</td>
<td>0.10</td>
</tr>
<tr>
<td>High-risk</td>
<td>4.57 (2.00-10.44)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Conditioning regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traditional ablative</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>RIC</td>
<td>1.37 (0.96-1.94)</td>
<td>0.07</td>
</tr>
<tr>
<td>Therapy-Related Disease</td>
<td>2.21 (1.42-3.44)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
NCCN: APPROACHES FOR MANAGEMENT OF MDS

- Clinically Relevant Cytopenia(s)
- Age: > <60 years old
- Performance Status: Excellent, Good, Poor
- Prognostic Risk Category (IPSS/WPSS/IPSS-R):
  - Lower risk (VL,L,Int): Hematologic improvement
  - Higher risk (Int,H,VH): Alter disease natural history

- HSCT candidate: Prognostic Risk Category, Age, PS, Donor

(JNCCN 11:838, 2013; www.nccn.org)
Cytogenetic Impact post AzaC Treatment
Sebert et al, Proc ASH #389, n=389, US, Italy, France

• 66% w/ abnormal karyotype
• IPSS-R Cytogenetics groups: 1,4,17, 35,43%
• Clinical Outcomes:
  – Heme Response 41%, 13%CR: ↑+8, 5q-; ↓3q26
  – OS 16.5 mo median: ↓17p-, -7/7q-, 5q-
  – Cytogenetic response (32%) ≠ outcome
• Basal cytogenetics generally not predictive
  ➔ Other features play critical roles
MDS: Cryptic (Cyto)genetic Δ/Unsuccessful Metaphase Cytogenetics

• Δ SNP-A vs MC (78% v 59%): CNA, LOH, UPD
  – SNP-A replicated prior MC lesions
• Δ SNP-A in 58% w/ Normal MC
• Δ SNP-A in 50% with unsuccessful MC
  – impact on IPSS/IPSS-R for OS evaluation
  – Present within PB as well as BM DNA

MDS: Recurrent Gene Mutations Associated with Poor Prognosis

- Signaling/different’ n
- Cell cycle regulators
- Apoptosis
- Translation
- Transcription
- Epigenetic regulators

- RAS §, RUNX1* § ^, ETV6* § ; FMS, FLT3, SETBP1, CUX1
- TP53* §, NPM1 §
- BCL2, BCOR
- RPS14;L23,S4X,S25,S19
- mRNA splicing: SF3B1nm, SRSF2nm^ 
- ASXL1*^ §, EZH2* § ^; TET2nm § ^, DNMT3A

*Bejar et al, NEJM 2011
§ Haferlach et al, Leuk 2014
^also for CMML
¶Modified from Greenberg, JNCCN 11:877, 2013
Clinical Impact of TP53 Mutations in MDS
Kulasekaranraj et al, BJHaem 2013

OS: All Patients
- Wild type TP53 (N = 288)
- Mutant TP53 (N = 30)

PFS: All Patients
- Wild type TP53 (N = 268)
- Mutant TP53 (N = 25)

OS: Poor Risk Cytogenetics
- Wild type TP53 (N = 45)
- Mutant TP53 (N = 22)

OS: 5q- alone
- Wild type TP53 (N = 21)
- Mutant TP53 (N = 5)
LFS Relative to Number of Oncogenic Mutations
Papaemmanuil et al, Blood 2013, n= 595

Graph showing the relationship between Leukemia-free survival and the number of driver mutations identified. The graph indicates that as the number of mutations increases, Leukemia-free survival decreases. There are significant differences in survival rates among different mutation categories, with a p-value of < 0.0001. The categories include:
- 0 driver mutations identified (n=116)
- 1 driver mutations identified (n=138)
- 2 driver mutations identified (n=167)
- 3 driver mutations identified (n=111)
- 4-5 driver mutations identified (n=50)
- ≥6 driver mutations identified (n=13)
Mesenchymal Stromal Cell Density in MDS

R Johnson et al, Proc ASH #1560, n=61

- Marrow biopsy tissue microarray analysis
  - IHC w/ CD271+ MSC

- MSC density ↑ in MDS/↑ CXCL12 expression
  - CXCL12 → HSC trafficking/retention

- MSC in direct contact w/ CD34+ cells
  - Associated w/ higher risk disease (IPSS-R), 2º MDS
  - ↓ overall survival
  - Possible abnormal feedback loop between a dysfunctional mesenchymal niche and HPSCs
Future Risk-Based Classification Systems for MDS

- Add/evaluate further prognostic features in larger & coalesced patient cohorts
  - Molecular: single, combinations, evolutionary (IWG-PM collaborative study)
  - Cytogenetic adjuncts: SNP-A, FISH
  - Flow cytometric: lineage infidelity, coexpression
  - Microenvironmental: inflammatory Δ, niche
- Integrate these features for 1° & 2° disease classification/mgt/clinical trials