Revised International Prognostic Scoring System (IPSS-R): Developed by the International Working Group for Prognosis in MDS (IWG-PM)

MDS Symposium, ASH December 2011

Peter Greenberg, MD
Stanford University Cancer Center
for the IWG-PM
MDS Classifications

- 1997 IPSS/IMRAW (FAB): 816 pts/7 DBs
  - Marrow blasts, cytogenetics, cytopenias
- 2001 WHO classification
  - Dysplastic subgroups, RAEB-1,2, del(5q)
- 2007 WPSS: 1165 pts/3 DBs
  - WHO subgroups, IPSS cytogenetics, RBC Txns
- 2001-2011 New features described as possible additional prognostic factors
- New cytogenetic classification: 2900 pts/4 DBs
- 2011 IWG-PM Refined consensus system (IPSS-R)
  - 7012 pts/18 DBs
IWG-PM: Aims for Refining IPSS

- Determine impact of newer features for prognostic power
- Incorporate larger cytogenetic subgroups & Re-assess their prognostic impact
- Analyze depth of cytopenias
- Provide better prognostic ability
- Maintain continuity, feasibility, flexibility
IWG-PM
Tuechler, Haase, Schanz, Greenberg
Cytogenetic Committee, PIs confirm DBs

- Vetted DBs from 18 institutions → Combined DB
  -- 1^0 untreated, accuracy, completeness, cytogenetics, outcomes
- Further assessed cytogenetics: standard ISCN
  - Cytogenetic Committee review
- Data review, statistical weighting for predictive power
- Data analysis
- Final IPSS-R model generated
IWG-PM: Inclusion criteria

• Primary MDS (FAB or WHO)
  – Marrow blasts ≤30%; PB blasts ≤19%
  – WBC ≤12,000/mm³ (ANC ≤8,000)
  – ≥2 months stable disease
• Marrow blasts, Cytogenetics, Hb, ANC, Platelet levels documented
• No disease-altering therapy during chronic phase
• Valid survival data
• Age ≥16yo
## IWG-PM Database PIs

12 countries/18 DBs, n=7012

<table>
<thead>
<tr>
<th>Country</th>
<th>City</th>
<th>PI</th>
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<tbody>
<tr>
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<td>Sanz, Sole, Vallespi</td>
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<td>Dusseldorf</td>
<td>Germing</td>
<td>USA-MD Anderson</td>
<td>Garcia-Manero Sekeres</td>
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<td>Luebbert</td>
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<td>Haase</td>
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<td>Alessandria</td>
<td>Levis</td>
<td>IMRAW</td>
<td>Greenberg Bennett</td>
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<td>Pavia</td>
<td>Cazzola</td>
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<td></td>
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<td>Malcovati</td>
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</table>
Combined DB--Variables (1)

- 7012 pts from 18 DBs
- Age 71yo (median), M:F 1.5:1
- Followup time 3.9yr, median
- FAB 7000 pts; WHO 5504 pts (79%); WPSS 2325 pts (33%)
  - RAEBT 6%, CMML 9%, 5q- 4%
- Ferritin 43%; RBC Txn Dept 13% (32% w/ data)
- BM fibrosis 19%, LDH 61%, B2M 13%, PS-ECOG 36%
Combined DB--Variables (2)

- **Cytogenetics, n=7001**
  - IPSS Good/Int/Poor 75/13/12% (‘97: 74/15/11)
  - IPSS-R: V Good/Good/Int/Poor/V Poor: 4/72/13/4/7%

- **IPSS categories, n=7008**
  - Low/Int1/Int2/High 37/40/16/7%  
    (‘97: 33/38/22/7)

- **WPSS categories, n=2325**
  - 22/32/20/20/4%  
    (‘07: 23/28/19/23/7)
IPPS-R: Cytogenetic Prognostic Subgroups

- **Very Good**: del(11q), -Y
- **Good**: +11, del(20q), del(5q) alone and double, del(12p)
- **Intermediate**: +8, 7q-, i(17q), +19, +21, any other single or double, independent clones
- **Poor**: der(3)q21/q26, -7, double including 7q-, Complex (3 abnormalities)
- **Very Poor**: Complex (>3 abnormalities)

Schanz et al, J Clin Oncol, in press
IPSS-R:
Statistical Weights of Predictive Variables
## IPSS-R for MDS: Prognostic Score Values*

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>1.5</th>
<th>1.5</th>
<th>2.5</th>
<th>3.5</th>
<th>5</th>
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<tbody>
<tr>
<td><strong>Cyto</strong></td>
<td>Very Good</td>
<td>Good</td>
<td></td>
<td></td>
<td>Int</td>
<td>Poor</td>
<td>Very Poor</td>
</tr>
<tr>
<td><strong>Blasts</strong></td>
<td>&lt;5%</td>
<td></td>
<td>5-10%</td>
<td>11-30%</td>
<td></td>
<td></td>
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<tr>
<td><strong>Hb</strong></td>
<td>≥10</td>
<td></td>
<td></td>
<td>&lt;10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plt</strong></td>
<td>≥100</td>
<td></td>
<td>&lt;100</td>
<td></td>
<td></td>
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<tr>
<td><strong>ANC</strong></td>
<td>≥0.8</td>
<td>&lt;0.8</td>
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</tbody>
</table>

*Regression analysis for survival and AML evolution*
Prognostic Risk Groups/Scores*

1. Very Low: 0 - 2
2. Good: >2 - 3.5
3. Intermediate: >3.5 - 5
4. High: >5 - 6
5. Very High: >6

*Values for 70yo patient
For consideration of age:
(age in yrs - 70) x 0.04, add result to sum of other variables
IPSS Freedom from AML Transformation

n=7008

Dxy 0.48

Months
IPSS Survival, n=7008

Dxy 0.37
IPSS-R Freedom from AML Transformation

n=7012

Fraction of patients

Dxy 0.5

Months
IPSS-R Survival, n=7012

Fraction of patients

Months

Dxy 0.43

very good
good
int
poor
very poor
IPSS-R: Survival ≤60 vs >60 yo
## IPSS-R: Prognostic Subgroup Clinical Outcomes*

<table>
<thead>
<tr>
<th></th>
<th>1 Very Low</th>
<th>2 Good</th>
<th>3 Intermediate</th>
<th>4 Poor</th>
<th>5 Very High</th>
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<tr>
<td><strong>OS</strong></td>
<td>8.7</td>
<td>5.3</td>
<td>3.0</td>
<td>1.6</td>
<td>0.8</td>
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<tr>
<td><strong>AML, 25%</strong></td>
<td>NR</td>
<td>10.7</td>
<td>4.0</td>
<td>1.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Medians, years
WPSS-R Freedom from AML Transformation
n=2325

Dxy 0.53

Months

VERY LOW
LOW
INTER
HIGH
VERY HIGH
WPSS-R Survival, n=2325

Dxy 0.42

Months
# IPSS-R: Additive Prognostic Variables*

<table>
<thead>
<tr>
<th></th>
<th>Total cases</th>
<th>Survival</th>
<th>AML</th>
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</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>B2M</td>
<td>15%</td>
<td>(++)</td>
<td>-</td>
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</table>

*Based on p<.05 & gain in Dxy concordance coefficient/predictive value (Cox proportional hazard models)
IPSS-R, WPSS-R: Advances Beyond the IPSS & WPSS

• Added refined cytogenetic subgroups (16 vs 7) & prognostic categories (5 vs 3)
• Analyzed depth of cytopenias
• Improved predictive power w/ more precise prognostic subgroups (5 vs 4)
• Clear impact of age and additional predictive features for survival
  – PS, ferritin, LDH
IWG-PM Directions

- Morphologic review of ‘low blast’ dysplasia
  - Further evaluation of WPSS-R
- Web-based calculator tool
- Resource for the field
- IPSS-R/Molecular-1,-2
  - Impact of molecular lesions on the IPSS-R
- Dynamic IPSS-R
- IWG-PM for Treated and 2₀ MDS pts