Myelodysplastic Syndromes: Molecular & Clinical Classifications

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Tel Aviv MDS Foundation Meeting
March 2020
Disclosures

• Novartis—Advisory Group
• Celgene—Research funds
• H3 Biotech
• Aprea
• Notable Labs
MDS Classification: Trajectory

• Prior systems
  • Characterization: Morphology—dysplasia, marrow blast %
  • Classification: Clinical prognostic risk-based analyses
    • Morphology/CBC/Cytogenetics codified/quantified
    • IPSS 1997; IPSS-R 2012; WPSS-R 2015
  • Mutations 2011 – present
    • Type, number, allelic status, co-mutations

• Molecular variables as complement to clinical features
  • Cytogenetic abnormalities in only ~50% MDS patients
  • Numerous mutational subtypes often with low incidence
  • Multiple co-mutations influencing clinical outcomes

→ IPSS-R/Molecular project
## MDS Classifications 1982-97

<table>
<thead>
<tr>
<th>System</th>
<th>BM Blasts</th>
<th>Cytopenias</th>
<th>Cyto-genetics</th>
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| Individuum   | SARS-CoV  
SARS-CoV_PC4-227  
SARSr-CoV_BtKY72  
SARS-CoV-2/X1/Human/2019/Wuhan_XYZ12345 |
Severe acute respiratory syndrome-related coronavirus: Species & its Viruses


Coronavirus Study Group
# Prognostic Classification Systems for MDS & CMML 1997-2013

<table>
<thead>
<tr>
<th>IPSS</th>
<th>Blasts</th>
<th>Cyto</th>
<th>Hgb</th>
<th>Plts</th>
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</table>

1 WHO MDS subtype  
2 RBC transfusion dependency can be substituted by hemoglobin (Hgb) level  
3 Leukocytosis  
4 CMML: FAB and WHO MDS subtypes  
5 Plus other variables: LDH, ferritin, β2-microglobulin, fibrosis

*Jonas & Greenberg, 2015*
Revised International Prognostic Scoring System (IPSS-R)

**Cytopenias, Cytogenetics, Marrow blasts**

**Calculate risk score**
- **Cytogenetics**
  - normal: del(20), del(22q) alone or with other anomaly: del(12p)
  - +8, del(7q), +17q, +19, -17: any single or double abnormality not listed
  - two or more independent clones: der(3q), -7, double with del(7q), complex with 3 abnormalities
  - complex with > 3 abnormalities

**Marrow blasts**
- <= 2%
- > 2% - < 5%
- 5% - 10%
- > 10%

**Bone marrow blast %**
- 0
- 1
- 2
- 3

**Hemoglobin (g/dL)**
- >= 10
- 6 - < 10
- < 6

**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**
- Total score
- % of patients
- Median survival, years
- Time to 25% with AML, years
- IPSS-R risk group

**Graphs**
- Overall survival, years
- Time to AML evolution, years

*Greenberg et al, IWG-PM, Blood 2012, n=7012*
t-MDS & IPSS-R: Clinical Outcomes

Ok CY et al, Leukemia 28:185, 2014; n=411
(MDA & MGH)
MDS: Post-Allogeneic HSC Transplant Outcome: OS Relation to Pre-Transplant IPSS-R Risk Category

GITMO study, n=519, Della Porta et al, Blood 2014
MDS mutations across pathways

- **Splicing factors**: SF3B1, SRSF2, U2AF1, ZRSR2
- **DNA methylation**: TET2, DNMT3A, IDH1/2
- **Histone modification**: ASXL1, EZH2, BCOR, EP300
- **Cohesin components**: STAG2, RAD21, SMC1A, SMC3
- **Transcription factors**: RUNX1, ETV6, CUX1, GATA2
- **Signal transduction**: CBL, JAK2, NRAS, KRAS, MPL, NF1, PTPN11, KIT, FLT3
- **p53 pathway**: TP53, PPM1D

References:
- Kennedy and Ebert JCO 2017
- Sperling et al Nature Rev 2017
- Saez et al Blood 2017
- Haferlach at al Leukemia 2014
- Yoshida et al Nature 2011
- Papaemmanuil et al NEJM 2011
Mutation Impact on Survival in MDS --additive to IPSS-R categories*

*TP53, ASXL1, RUNX1, EZH2, ETV6
Bejar et al, Haematologica 2014
LFS Relative to Number of Oncogenic Mutations

Papaemmanuil et al, Blood 2013; n = 595

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)

Leukemia-free survival

Time (months)

p < 0.0001
Genomic population studies identify molecular prognostic markers

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Authors</th>
<th>Year</th>
<th>Prognostic genes in multivariate model</th>
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<tbody>
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<td>439</td>
<td>Bejar et al.</td>
<td>2011</td>
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<td>EZH2, DNMT3A, SF3B1, SRSF2, RUNX1, TET2, TP53</td>
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<td>944</td>
<td>Haferlach et al.</td>
<td>2014</td>
<td>ASXL1, KRAS, LAMB4, NPM1, PRPF8, RUNX1, TP53</td>
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<td>508</td>
<td>Nazha et al.</td>
<td>2017</td>
<td>CBL, NRAS, TP53</td>
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<td>685</td>
<td>Tefferi et al.</td>
<td>2018</td>
<td>ASXL1, SF3B1, RUNX1</td>
</tr>
</tbody>
</table>
Post Allo-Transplant Clinical/Molecular Model

Della Porta et al, J Clin Oncol '16, GITMO, n=401 MDS/AML-MRC
5 Independent Predictors including ASXL1, RUNX1, TP53 mutations
MDS Classification: Project update

• Biologic variables needed to complement clinical features
  • Cytogenetic abnormalities in only ~50% MDS patients
  • Numerous mutational subtypes often with low incidence
  • Multiple co-mutations influencing clinical outcomes

• Robust integrated clinical-molecular database and sequencing program required
  • IPSS-R/Molecular project through the IWG-PM under the aegis of the MDS Foundation, n = 3000+ samples
  • Sequencing @ Memorial Sloan Kettering—E Papaemmanuil, E Bernard
    • Coordinating Committee: Bejar, Cazzola, Ebert, Greenberg, Hellstrom, Malcovati, Ogawa
International Working Group for the prognosis of MDS

13 countries | 25 centers
Survival Impact of Mutant Driver Numbers

E Bernard et al, for IWG-PM, MDS Fndn Symposium, ASH 2018
Long tail of gene frequency with co-mutators

E Bernard et al, for IWG-PM, MDS Fndn Symposium, ASH 2018
MDS Mutational Analyses: Co-Mutation Map (n=1672)

Haferlach at al Leukemia 2014
Pammananui et al Blood 2013
Incorporation of SF3B1 status in WHO 2016

**MYELOID NEOPLASIA**

*SF3B1* mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts

Luca Malcovati,1,2 Mohsen Karimi,3 Elli Papaemmanuil,4 Ilaria Ambaglio,2,5 Martin Jädersten,6 Monika Jansson,3 Chiara Elena,1,2 Anna Galli,2 Gunilla Waldin,2 Matteo G. Delia Porta,2,6 Kias Raaschou-Jensen,6 Erica Travaglino,2 Klaus Kallenbach,7 Daniela Pietra,8 Viktor Ljungström,9 Simona Conte,8 Emanuela Boven,9 Rosangela Invernizzi,2,10 Richard Rosenquist,8 Peter J. Campbell,1 Mario Cazzola,1,9 and Eva Hellström Lindberg7

WHO 2016 MDS-RS:
more than 15% ringed sideroblasts
Or
more than 5% of ringed sideroblasts and SF3B1 mutation

BLOOD, 8 DECEMBER 2011 • VOLUME 118, NUMBER 24

**WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues**

Figure 2. Relationship between SF3B1 mutant allele burden and proportion of ring sideroblasts. Values for percentage of ring sideroblasts are grouped here in 3 arbitrary categories: <15% (n = 168), 15% to 50% (n = 85), and >50% (n = 57). Data are shown in a box plot depicting the smallest and largest observation (lowest and highest horizontal line, respectively), lower and upper quartile with median value (box), and outliers (dots).

Malcovati et al Blood 2011
Papaemmanuil et al NEJM 2011
mSF3B1 Outcome Shift with Co-Mutators

E Bernard et al, for IWG-PM, MDS Fndn Symposium, ASH 2018
**TP53 Allelic State Shapes 1° MDS Clinical Outcomes**

68% multi-hit/bi-allelic mTP53

*Bernard et al, for IWG-PM, ASH 2019, #675*
TP53 Allelic State Impacts IPSS-R Risk Group Survival Outcomes

Bernard et al for IWG-PM, ASH2019 #675
Patient TP53 Status: 368 mutated, 2780 Wild-type
TP53 Allelic State Shapes Clinical Outcomes in Therapy-Related MDS & HMA Response

1° & Therapy-Related MDS

Impact of HMA Therapy

Bernard et al for IWG-PM, ASH 2019, #675
MDS Molecular and Clinical Classification

Summary

• Better defined:
  • Molecular heterogeneity
  • Mutations: critical nature of allele status, number and co-mutators
  • Impact on survival, AML evolution, HMA responses
  • Both p- and TR-MDS evaluated

• IPSSR-Molecular classification project progressing
  • Genotype-Phenotype associations for clinical subtypes
  • Identifying VUSs as now being pathogenic
  • Prognostic classification
  • Ongoing analysis of potential therapeutic targets
  • Other features to be integrated (e.g., gene expression)