Myelodysplastic Syndromes: Disease, Diagnosis, & Treatment

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Myelodysplastic Syndrome
Myelodysplastic Syndrome = bone marrow cells = funny looking = group of symptoms
Picasso Premise
Picasso

Guitar on a Table
Normal Bone Marrow
4 pathologists walk into a room ...

- myeloid
- megakaryocyte
- erythroid
4 pathologists walk into a room …

- myeloid: 89% agreement
- megakaryocyte: 91% agreement
- erythroid: 75% agreement
Incidence of MDS

Cogle, et al. Leukemia Research 2014
Incidence of MDS

3.3 out of 100,000

Cogle, et al. Leukemia Research 2014
Incidence of MDS

3.3 out of 100,000

Cogle, et al. Leukemia Research 2014
3.3 out of 100,000 Incidence of MDS

5.3 out of 100,000 Incidence of MDS

Cogle, et al. *Leukemia Research* 2014
Incidence of MDS ≥ 65

20 out of 100,000

Cogle, et al. Leukemia Research 2014
Incidences of MDS ≥ 65

20 out of 100,000

75 out of 100,000

Cogle, et al. Leukemia Research 2014
MDS

10,000 people diagnosed each year in US

60,000 - 170,000 MDS currently in US
Software Bugs
Chromosomes

Genes

DNA
Chromosomes

↓

Genes

↓

DNA
MDS Chromosomes

deletion 5q

lenalidomide (Revlimid)
MDS Chromosomes

deletion 5q

“normal”

lenalidomide (Revlimid)

50% of MDS patients
MDS Gene Mutations

MDS Gene Mutations

78% of patients had at least 1 gene or chromosome abnormality

MDS Gene Mutations

Risk of Death and Progression to AML

## MDS Gene Mutations

### Risk of Death and Progression to AML

<table>
<thead>
<tr>
<th>Gene</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EZH2</td>
<td>Univariate model</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Model with adjustment for IPSS</td>
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<tr>
<td>TP53</td>
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<td>Model with adjustment for IPSS</td>
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<td>RUNX1</td>
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<td>Model with adjustment for IPSS</td>
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<td>NRAS</td>
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<td>Univariate model</td>
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<td>Model with adjustment for IPSS</td>
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</tbody>
</table>

Current Thinking in MDS

**IPSS-R Scoring System**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Categories and Associated Scores</th>
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<tbody>
<tr>
<td>Cytogenetic risk group</td>
<td>Very good</td>
</tr>
<tr>
<td>≤2%</td>
<td>0</td>
</tr>
<tr>
<td>&gt;2% to &lt;5%</td>
<td>1</td>
</tr>
<tr>
<td>5% to 10%</td>
<td></td>
</tr>
<tr>
<td>&gt;10%</td>
<td></td>
</tr>
<tr>
<td>Marrow blast proportion</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10 g/dL</td>
</tr>
<tr>
<td>≥10 g/dL</td>
<td>0</td>
</tr>
<tr>
<td>8 to &lt;10 g/dL</td>
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</tr>
<tr>
<td>&lt;8 g/dL</td>
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<tr>
<td>Absolute neutrophil count</td>
<td>≥0.8 × 10^9/L</td>
</tr>
<tr>
<td>≥0.8 × 10^9/L</td>
<td>0</td>
</tr>
<tr>
<td>&lt;0.8 × 10^9/L</td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>≥100 × 10^9/L</td>
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<tr>
<td>≥100 × 10^9/L</td>
<td>0</td>
</tr>
<tr>
<td>50 to &lt;100 × 10^9/L</td>
<td></td>
</tr>
<tr>
<td>&lt;50 × 10^9/L</td>
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</tr>
</tbody>
</table>

Current Thinking in MDS

**IPSS-R Chromosome Scoring**

- **Very good**
  - n=81 (2.9%)
  - Single del(11q) -Y
    - Single del(5q) del(12p) del(20q)
    - Double incl. del(5q)

- **Good**
  - n=1809 (65.7%)
  - normal
    - Single del(7q) +8 i(17q) +19 any others indep. clones
    - Double any other

- **Intermediate**
  - n=529 (19.2%)
  - Single der(3q) -7
    - Complex incl. -7/7q-
    - Double 3 abnormalities

- **Poor**
  - n=148 (5.4%)
  - Very Poor n=187 (6.8%)
  - Complex >3 abnormalities

MDS Gene Mutations

Old News

MDS Gene Mutations

Old News

New News

A

Low risk (N=110)
Intermediate-1 risk (N=185)
Intermediate-2 risk (N=101)
High risk (N=32)

C

Low risk, mutation absent (N=87)
Low risk, mutation present (N=23)
P<0.001
Intermediate-1 risk (N=185)

MDS Gene Mutations
Response to Lenalidomide

TP53 mutation
normal TP53

Caceres, et al. PNAS 2013
MDS Gene Mutations
Response to Azacitidine

MDS Gene Mutations
Response to Azacitidine

2 x more likely to achieve response

MDS Gene Mutations

Response to Transplant

Old News

MDS Gene Mutations
Response to Transplant

Old News

New News

A

C

Overall Survival (probability)

Overall Survival (probability)

Time (months)

Time (months)

Not complex (n = 59)
Complex karyotype (n = 28)

TP53 mutated (n = 18)
TET2 mutated, no TP53 (n = 10)
DNMT3A mutated, no TP53 or TET2 (n = 12)
No TP53, TET2, or DNMT3A mutations (n = 47)

$P = .005$
Current Thinking in MDS
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Current Thinking in MDS
Clone Wars
Quiet Beginnings
MDS Gene Mutations

MDS Gene Mutations in the General Population
MDS Gene Mutations in the General Population

Normal Tissue

Cancer Tissue

Nordling. Br J Cancer 1953
Knudson. PNAS 1971
Multi-Hit Hypothesis

Nordling. Br J Cancer 1953
Knudson. PNAS 1971
Absentee Parenting
Hematopoietic Stem Cell
Hematopoietic Stem Cell

Self Renewal
Hematopoietic Stem Cell

Self Renewal

Multi-Lineage Differentiation
Hematopoietic Stem Cell

Self Renewal  Multi-Lineage Differentiation  Quiescence
Bone Marrow Stem Cells
Bone Marrow Stem Cells
Bone

Blood Vessels

Bone
Bone

Blood Vessels

Bone

Thank you

1. Picasso Premise
2. Software Bugs
3. Clone Wars
4. Quiet Beginnings
5. Absentee Parenting