MDS under the age of 50

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DISCLOSURE

I have no relevant financial relationships to disclose.
Pre-test audience response question

What proportion of patients diagnosed with MDS between the ages of 18 and 50 have an underlying germline predisposition syndrome?

1. <5%
2. 5-9%
3. 10-20%
4. >30%
Outline

• Case
• Epidemiology
• Disease characteristics
• Role of inherited predisposition
• Prognosis & Treatment differences
Case

- 33 year old female presents with pancytopenia
- WBC 3.2 g/dL, Hgb 10 g/dL, MCV 107, Platelets 95,000/uL, ANC 1.7 K/uL
- BM Biopsy:
  - 40% cellular, no dysplasia, no increase in blasts, no ringed sideroblasts
  - Karyotype: 46,XX,del(5)(q15q31)[15]/46,XX,del(13)(q12q14)[6]
Diagnosis:

Karyotype image: atlasgenesicsoncology.org/Anomalies/del5qSoleID1134.html
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Blood</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with single lineage dysplasia (MDS-SLD)</td>
<td>Single or bicytopenia</td>
<td>Dysplasia in ≥10% of one cell line, &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with ring sideroblasts (MDS-RS)</td>
<td>Anemia, no blasts</td>
<td>≥15% of erythroid precursors w/ ring sideroblasts, or ≥5% ring sideroblasts if SF3B1 mutation present</td>
</tr>
<tr>
<td>MDS with multilineage dysplasia (MDS-MLD)</td>
<td>Cytopenia(s), ≤1 x 10^9/L monocytes</td>
<td>Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, &lt;15% ring sideroblasts (or &lt;5% ring sideroblasts if SF3B1 mutation present), &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with excess blasts-1 (MDS-EB-1)</td>
<td>Cytopenia(s), ≤2%–4% blasts, ≤1 x 10^9/L monocytes</td>
<td>Unilineage or multilineage dysplasia, 5%–9% blasts, no Auer rods</td>
</tr>
<tr>
<td>MDS with excess blasts-2 (MDS-EB-2)</td>
<td>Cytopenia(s), 5%–19% blasts, ≤1 x 10^9/L monocytes</td>
<td>Unilineage or multilineage dysplasia, 10%–19% blasts, ± Auer rods</td>
</tr>
<tr>
<td>MDS, unclassifiable (MDS-U)</td>
<td>Cytopenias, ±1% blasts on at least 2 occasions</td>
<td>Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>Anemia, platelets normal or increased</td>
<td>Unilineage erythroid dysplasia, isolated del(5q), &lt;5% blasts ± one other abnormality except -7/del(7q)</td>
</tr>
<tr>
<td>Refractory cytopenia of childhood</td>
<td>Cytopenias, &lt;2% blasts</td>
<td>Dysplasia in 1–3 lineages, &lt;5% blasts</td>
</tr>
</tbody>
</table>

NCCN Guidelines Version 1.2020
How common is MDS in this age group?
Good Question: MDS epidemiology data limitations

• Cancer registries & MDS:
  • US: SEER 2001
  • Sweden: 1993

• Under-reporting

• Changing classifications, therapy-related cases

Ma X. Am J Med 2012;125(7 suppl):S2-S5
MDS across the life spectrum: SEER 2001-2008

- **Pediatric:** 1 case per million persons per year
- **Young adult:** 1 to 10 cases per million persons per year
- **Older adults:** 20 to 50 cases per 100,000 persons at risk

Median = 72 years old

Ma X. Am J Med 2012;125(7 suppl):S2-S5
SEER 2012-2016: Her case is one in a million

### Myelodysplastic Syndromes (MDS) By Age at Diagnosis

<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>Both Sexes</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>Count</td>
<td></td>
</tr>
<tr>
<td>Ages &lt;40</td>
<td>0.1</td>
<td>438</td>
<td></td>
</tr>
<tr>
<td>Ages 40-49</td>
<td>0.7</td>
<td>549</td>
<td></td>
</tr>
<tr>
<td>Ages 50-59</td>
<td>2.1</td>
<td>1,764</td>
<td></td>
</tr>
<tr>
<td>Ages 60-69</td>
<td>8.2</td>
<td>4,868</td>
<td></td>
</tr>
<tr>
<td>Ages 70-79</td>
<td>26.9</td>
<td>8,579</td>
<td></td>
</tr>
<tr>
<td>Ages 80+</td>
<td>55.4</td>
<td>11,940</td>
<td></td>
</tr>
</tbody>
</table>

**Age <50:**
- 1 to 7 new cases per million persons at risk per year
- 4-7% of all MDS cases

Do MDS cases in young adults have the same disease features as that in older adults?
Primary MDS: characteristics overall similar

<table>
<thead>
<tr>
<th></th>
<th>Young Adult (18-49)</th>
<th>Adult (50+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at onset</td>
<td>41</td>
<td>71</td>
</tr>
<tr>
<td>Gender predominance</td>
<td>Female</td>
<td>Male</td>
</tr>
</tbody>
</table>

Presenting blood counts, Blast counts, WHO subtype, IPSS, Karyotype distributions== SIMILAR

Chang et al Leukemia. 2002;16:623-631  
Kuendgen et al JCO. 2006;24(34):5358  
Al-Kali et al; JCO. 2017. e18560
## Pediatric MDS: more -7, most RCC

<table>
<thead>
<tr>
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<th>Pediatric (&lt;18)</th>
<th>Young Adult (18-49)</th>
<th>Adult (50+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age at onset</strong></td>
<td>7 to 8</td>
<td>41</td>
<td>71</td>
</tr>
<tr>
<td><strong>Gender predominance</strong></td>
<td>M=F</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td><strong>Karyotype</strong></td>
<td>-7 in 13-25%</td>
<td>-7/7q- 7-10%</td>
<td>-7/7q- 4-10%</td>
</tr>
<tr>
<td></td>
<td>Normal in 60%</td>
<td>Complex 9%</td>
<td>Complex 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal 53%</td>
<td>Normal 50%</td>
</tr>
<tr>
<td><strong>WHO subtype</strong></td>
<td>Most RCC, hypocellular</td>
<td>Subtype proportions similar</td>
<td></td>
</tr>
</tbody>
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Chang et al Leukemia. 2002;16:623-631  
Kuendgen et al JCO. 2006;24(34):5358  
Al-Kali et al; JCO. 2017. e18560
## More therapy-related MDS in young patients

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<th>Young Adult (18-49)</th>
<th>Adult (50+)</th>
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<tr>
<td>Therapy-related</td>
<td>16%</td>
<td>15-33%</td>
<td>5%-17%</td>
</tr>
</tbody>
</table>

49% in 1980s-1990s series

References:
- Kuendgen et al. JCO. 2006;24(34):5358
What about mutation status?
Healthy people have increases in blood cancer related variants with age

**Large Copy Number Variants**
- <0.5% by 50

**Single Nucleotide Variants**
- <3% by 50
- 10% by 80


Jaiswal et al. NEJM. 2014.371;26:2488-98
Genovese et al. NEJM. 2014.371;26:2477-87
Similarly, MDS cases have increased numbers of acquired mutations with age.

Significantly more SRSF2, TET2 with age
In contrast, TP53 more constant
Dominant acquired mutation patterns: *RUNX1, TP53* in young versus *TET2, STAG2* in older adults.

Acquired mutation spectrum differences: genes with germline potential more frequent in young adults

Lindsley et al. NEJM. 2017;376(6):536-547
If disease characteristics are overall similar, why would a young adult develop a disease of aging?
Multiple mutational events over time in different HSCs

Known risk factors: older patient

• AGE!
• Exposures (chemo, radiation, benzene, etc)
• Smoking
• Ethnicity (white > other)
• Gender (male)
MDS risk = mutational rate \times \text{time}
MDS risk = mutational rate $ \times $ time

AGE
MDS risk = \text{mutational rate} \times \text{time}

= \text{Mutagenic exposures} \times \text{Chemo (↑intensity= ↑risk)}
MDS risk = \text{mutational rate} \times \text{time}

= \text{Faster baseline mutational rate?}
Germline RUNX1 mutation carriers: 81% cumulative risk of CHIP by age 50
Similarly, 48% of patients with SDS (biallelic SBDS mutations) have CHIP by age 20 AND gene pattern differs

Xia et al. Blood. 2018;131(4):408-416
Familial MDS/AML due to biallelic $MBD4$ mutations: multiple $DNMT3A$ mutant clones early in life

Germline disorders change the rate and pattern of this process as an explanation for earlier onset disease.

MDS risk = $\text{mutational rate} \times \text{time}$

- Faster baseline mutational rate: Germline Predisposition
- Other?
Germline predisposition: many genes & pathways

Telomere maintenance

DNA repair

Immune function

Immune deficiency

Constitutional thrombocytopenia (CT)

DNA repair

Telomere maintenance

Immune function

Germline predisposition: many genes & pathways

What proportion of patients have germline predisposition?
Yield of germline testing in “sporadic” MDS

• Age <19 years: Cumulative estimates 30-50%
  • 28 of 426 (7%) = GATA2 deficiency
  • 8 of 46 (17%) = SAMD9/SAMD9L

• Age 18-50 years: Cumulative estimates 10-20%
  • 5 of 239 (2%) = Shwachman Diamond syndrome
  • 14 of 110 (13%) = 1 of 13 genes

• Age <50 vs Age 50+
  • 12% vs 4%

Lindsley et al NEJM. 2017. 376(6):536
Wlodarski et al Blood 2016. 127(11): 1387
Zhang et al Haematol. 2015.100(1):42
Schwartz et al Nat Commun. 2017;8:1557
Germline mutational patterns differ with age too

- **GATA2**
- **SAMD9/SAMD9L**
- **DDX41**

**Pediatric** → **Older adult**
Even within a gene, mutation type and effect may differ by age

What features suggest germ line predisposition in this age group?

Perform genetic testing on a germline sample.

Acquired mutation panel on MDS sample:
Pathogenic variant in GATA2 p.T354M VAF 45%
Caveats and challenges in young patients:

Many have no phenotypic features

MDS acquired panel may not be routine

Family history absent in 30-70%:
* incomplete penetrance
* autosomal recessive pattern
* young age of family

Wlodarski et al Blood 2016. 127(11): 1387
### WHO classification 2016

**Myelodysplastic syndromes (MDS)**
- MDS with single lineage dysplasia
- MDS with ring sideroblasts (MDS-RS)
  - MDS-RS and single lineage dysplasia
  - MDS-RS and multilineage dysplasia
- MDS with multilineage dysplasia
- MDS with excess blasts
- MDS with isolated del(5q)
- MDS, unclassifiable

*Provisional entity: Refractory cytopenia of childhood*

Myeloid neoplasms with germ line predisposition
Baseline dysplasia complicates diagnosis in germline predisposition syndromes: when to call MDS?

39 year old with FPD-AML

BM: hypocellular; isolated megakaryocytic dysplasia

Hasle et al Leukemia.2003;17:277-282
Questions that remain:

• How does a pathologist render a diagnosis pending germline evaluation (which may never be done)?

• Within this WHO 2016 germline category, are subtypes the same & where to fit t-MN?
How does age impact her prognosis?
### Prognosis

#### Median OS:
- IPSS-R = 8.8 year
- IPSS= 3.5 year

#### Variables (units) [usual range]

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL) [4-20]</td>
<td>10</td>
</tr>
<tr>
<td>A possible conversion for Hb values: 10 g/dL = 6.2 mmol/L, 8 g/dL = 5.0 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Absolute Neutrophil Count (x10^9/L) [0-15]</td>
<td>1.7</td>
</tr>
<tr>
<td>Platelets (x10^9/L) [0-2000]</td>
<td>95</td>
</tr>
<tr>
<td>Bone Marrow Blasts (percent) [0-30]</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Cytogenetic Category

- Good
- IPSS-R SCORE = 1.5
- IPSS-R CATEGORY = very low


Greenberg et al. Blood. 2012;120:2454
Age adjusted prognosis

n=1582 <60    Median age 71; n=5430 age >60

https://www.mds-foundation.org/calculator/index.php
Greenberg et al Blood.2012;120:2454
IPSS less discriminatory in low/intermediate I groups in young patients

Fig 4. Survival of patients younger than 50 years old according to the International Prognostic Scoring System.
Untreated patients:
Low/Int 1 IPSS MDS have significantly longer survival

Kuendgen et al. JCO. 2006;24(34):5358
For those that require transplantation: age x mutation status has survival implications.

Lindsley et al. NEJM. 2017;376(6):536-547.
Unique Treatment Considerations

• Tolerance of chemotherapy or preparative regimen
  • Usually more intensive so more important to identify germline syndromes

• Timing & Role of Transplantation
  • More life years at risk
  • More frequent predisposed HSC pool

• Survivorship
  • Long term toxicities (cardiovascular, reproductive, second cancers)
Conclusions

• MDS under age 50 is uncommon to rare
• Enriched for hereditary predisposition
• Prognosis for low/intermediate risk better than older adults
• Treatment considerations need to consider long term
What proportion of patients diagnosed with MDS between the ages of 18 and 50 have an underlying germline predisposition syndrome?

1. <5%
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3. 10-20%
4. >30%