Myelodysplastic Syndrome and Acute Myeloid Leukaemia: Overlap and differences

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Disclosure of speaker’s interests

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- (Potential) conflict of interest
- Consulting for Celgene and Agios
Introduction

• Myelodysplastic syndrome (MDS) is now recognized to be a clonal neoplasm that is more complex than simply representing “pre-leukemia”

• Some MDS types progress to acute myeloid leukemia (AML), but others are distinct with a relatively low rate of progression

• AML with myelodysplasia-related changes is closely linked to MDS, but some other AML subtypes are distinct from MDS
Overlap Between AML and MDS

- **Unique MDS types**
  - Ring sideroblasts
  - $SF3B1$ mutations, isolated 5q deletions

- **AML/MDS overlaps**
  - Multilineage dysplasia or erythroid predominance
  - Complex karyotype
  - $ASXL1$, $TP53$, $U2AF1$ mutations

- **Unique AML types**
  - $PML$-$RARA$, $RUNX1$-$RUNX1T1$, $CBFB$-$MYH11$, $NPM1$, or biallelic $CEBPA$ mutations
MDS Types Distinct from AML
MDS with ring sideroblasts (with or without multilineage dyplasia)

- Frequent association with mutations of SF3B1 and a favorable prognosis with low risk of transformation to acute leukemia
- WHO proposal:
  - >15% ring sideroblasts (among erythroid precursors), or
  - >5% in the presence of an SF3B1 mutation
  - Blast cell increases exclude this diagnosis

  • If multilineage dysplasia without a blast cell increase is present, case is classified as *MDS with ring sideroblasts and multilineage dysplasia*

MDS with Isolated del(5q) (5q-minus Syndrome)

- Currently restricted to del(5q) as the only abnormality
- Revision will now allow a second (except monosomy 7) cytogenetic abnormality
- Cases with >2 abnormalities will not qualify for this category
- Recommend TP53 mutation assessment or p53 staining

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AML Types Distinct from MDS
AML Entities in Which Blast Count Does not Matter

• Acute myeloid leukemia with t(8;21)(q22;q22.1); RUNX1-RUNX1T1

• Acute myeloid leukemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11

• Acute promyelocytic leukemia with PML-RARA
AML/MDS Overlaps

• AML with 20-29% blasts (RAEB-T)
• AML with myelodysplasia-related changes
• AML with t(6;9)(p23;q34.1); DEK-NUP214
• AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
• Therapy-related myeloid neoplasms
• Myeloid neoplasms of Down syndrome
Probability of Event Free Survival By Diagnosis

Low Blast Count AML

- Bone Marrow Pathology Group Study of 571 de novo AMLs in patients ≥ 50 years
  - 142 with 20-29% blasts (RAEB-T)
  - 429 with ≥ 30% blasts (AML30)
- Additional 151 patients with 10-19% blasts (RAEB-2)
- RAEB-T compared to AML30
  - Older
  - Lower WBC
  - Higher platelet and hemoglobin levels
  - Higher risk karyotypes
  - More frequent hypomethylating agents as first therapy

*De novo* acute myeloid leukemia with 20–29% blasts is less aggressive than acute myeloid leukemia with ≥30% blasts in older adults: a Bone Marrow Pathology Group study

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  – 142 with 20-29% blasts (RAEB-T)
  – 429 with ≥ 30% blasts (AML30)
• Additional 151 patients with 10-19% blasts (RAEB-2)
• Mutations
  – FLT3-ITD 4% of RAEB-T vs. 24% of AML30 (p<0.0001)
  – NPM1 2% of RAEB-T vs. 31% of AML30 (p<0.0001)
AML with Myelodysplasia-Related Changes

• Can only be diagnosed by morphology alone in the absence of *NPM1* or biallelic *CEBPA* mutations
Overall survival for patients classified according to dysplastic features following the World Health Organization categories.

Haferlach T et al. JCO 2003;21:256-265
NPM1 and CEBPA Mutations and Multilineage Dysplasia

- Significance of multilineage dysplasia in the presence of NPM1 mutation, a normal karyotype and no history of MDS
  - MLD found in 74/318 (23%) de novo NPM1 mutated AML
  - No prognostic significance for MLD

- CEBPA mutations
  - MLD found in 28/108 (25.9%) CEPBA mutated AML patients
  - No significant survival difference in MLD+ and MLD- groups

Survival curves of patients up to 60 years with intermediate-risk cytogenetics AML depending on *NPM1* status and presence of multilineage dysplastic features (MLD)

![Graph A](image)

- Mutated *NPM1*
- Survival probability over time
- Multilineage dysplasia
- No multilineage dysplasia

![Graph B](image)

- Wild-type *NPM1*
- Survival probability over time
- Multilineage dysplasia
- No multilineage dysplasia

AML with mutated *NPM1* or *CEPBA* and an abnormal karyotype

- Abnormal karyotype identified in 14.7% of *NPM1* and 26% of *CEBPA* mutated AML cases
- +8, +4, -Y, del(9q) and +21 most frequent with *NPM1* mutation
- del(9q), del(11q), -Y, +10, +21 most frequent with biallelic *CEBPA* mutation
- del(9q) is currently considered an MDS-related cytogenetic abnormality, but it appears to be unusually common in *NPM1* and *CEBPA* mutated cases
- In this setting, del(9q) does not appear to have prognostic significance

MDS-related cytogenetic abnormalities

- **Complex karyotype***
- **Unbalanced abnormalities**
  - -7/del(7q)
  - -5/del(5q)/t(5q)
  - i(17q)/t(17p)
  - -13/del(13q)
  - del(11q)
  - del(12p)/t(12p)
  - del(9q)
  - idic(X)(q13)

- **Balanced abnormalities**
  - t(11;16)(q23.3;p13.3)
  - t(3;21)(q26.2;q22.1)
  - t(1;3)(p36.3;q21.1.2)
  - t(2;11)(p21;q23.3)
  - t(5;12)(q32;p13.2)
  - t(5;7)(q32;q11.2)
  - t(5;17)(q32;p13.2)
  - t(5;10)(q32;q21)
  - t(3;5)(q25.3;q35.1)

***≥3 abnormalities
AML with Myelodysplasia-Related Changes

- Detection of multilineage dysplasia*
  - Two non-blast cell lines must show dysplasia in at least 50% of cells
- MDS-related cytogenetic abnormalities, or
- History of MDS or MDS/MPN
- Absence of the specific cytogenetic abnormalities of AML with recurrent genetic abnormalities
- Absence of prior history of therapy

* Cannot be used alone if NPM1 or biallelic CEBPA mutations are present
Genetics in MDS

• Somatic mutations in MDS
  – Prognostic significance of mutations of TP53, EZH2, ETV6, RUNX1, ASXL1 and others (Bejar R et al. NEJM 2011;364:2496)

Ribosomal proteins: RPS14
Epigenetic regulators: TET2, ASXL1
RNA splicing: SF3B1, SRSF2, U2AF1
Transcription factors: RUNX1, ETV6
Tyrosine kinase signaling: RAS
Tumor suppressor genes: TP53

MDS-associated genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency in MDS</th>
<th>Reported prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASXL1</td>
<td>15-25%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>RUNX1</td>
<td>10-15%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>TP53</td>
<td>8-12%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>EZH2</td>
<td>5-10%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>ETV6</td>
<td>&lt;5%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>SF3B1</td>
<td>18-30%</td>
<td>Favorable</td>
</tr>
<tr>
<td>TET2</td>
<td>20-25%</td>
<td>Neutral</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>12-18%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>SRSF2</td>
<td>10-15%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>U2AF1</td>
<td>8-12%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>ZRSR2</td>
<td>5-10%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>NRAS</td>
<td>5-10%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>SETBP1</td>
<td>&lt;5%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>IDH1</td>
<td>&lt;5%</td>
<td>Neutral</td>
</tr>
<tr>
<td>JAK2</td>
<td>&lt;5%</td>
<td>Neutral</td>
</tr>
<tr>
<td>CBL</td>
<td>&lt;5%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>IDH2</td>
<td>&lt;5%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>NPM1</td>
<td>&lt;5%</td>
<td>Neutral</td>
</tr>
<tr>
<td>IDH1</td>
<td>&lt;5%</td>
<td>Neutral</td>
</tr>
<tr>
<td>KRAS</td>
<td>&lt;2%</td>
<td>Neutral</td>
</tr>
<tr>
<td>GNAS</td>
<td>&lt;2%</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

In **BOLD** are genes that affect OS independent of IPSS and have been confirmed in multiple multivariate studies.

In *ITALICS* are genes where the reported prognostic impact will require further confirmation and/or evaluation in multivariate models that account for IPSS.
## Mutations in AML with Intermediate-Risk Cytogenetics

<table>
<thead>
<tr>
<th>Gene</th>
<th>AML-MRC</th>
<th>AML, NOS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASXL1</td>
<td>47%</td>
<td>0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RUNX1</td>
<td>22%</td>
<td>8%</td>
<td>0.087</td>
</tr>
<tr>
<td>TET2</td>
<td>17%</td>
<td>14%</td>
<td>0.480</td>
</tr>
<tr>
<td>IDH1</td>
<td>3%</td>
<td>8%</td>
<td>0.318</td>
</tr>
<tr>
<td>IDH2</td>
<td>28%</td>
<td>16%</td>
<td>0.181</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>6%</td>
<td>38%</td>
<td>0.001</td>
</tr>
<tr>
<td>NPM1</td>
<td>11%</td>
<td>62%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FLT3</td>
<td>3%</td>
<td>49%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Other AMLs with Dysplasia

- AML with \textit{t}(6;9)(p23;q34.1); \textit{DEK-NUP214}

- AML with \textit{inv}(3)(q21.3;q26.2) or \textit{t}(3;3)(q21.3;q26.2); \textit{GATA2, MECOM}
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM

- Bone Marrow Pathology Group study of 103 patients
  - MDS n=40
  - AML n=63
- 83% dead at 8 months
- Blast count not predictive of behavior
- Poor prognostic indicators on MVA
  - Complex karyotype
  - Monosomal karyotype
  - Dysgranulopoiesis

Therapy-Related Myeloid Neoplasms

Alkylating agent-related

Topo-II inhibitor-related
Lack of Significance of Blast Count in Therapy-Related Myeloid Neoplasms

Erythroid-Rich Myeloid Neoplasms
Erythroid-Rich Myeloid Neoplasms

• Several studies have now shown a worse prognosis in both AML and MDS when erythroid precursors predominate (see Arber DA. Curr Opin Hematol 24:146, 2017)

• Suggest that the erythroid/myeloid type of AML, NOS (erythroleukemia) may be similar to erythroid rich MDS

Acute erythroid leukemia (erythroid/myeloid type) proposed to become MDS with excess blasts

• 2008 definition of acute erythroleukemia (erythroid/myeloid type) in AML, NOS required ≥50% marrow erythroid precursors and ≥20% myeloblasts among non-erythroid cells

• These cases will now be classified as MDS based on the total blast cell count

Acute Erythroid Leukemia

Erythroleukemia (erythroid/myeloid type)
MDS with excess blasts

Pure erythroid leukemia
AML with Erythroid Predominance: Are All Cases MDS-Related?

- Studied 41 cases of AML with > 50% marrow erythroid precursors and 20% or more marrow or peripheral blood blasts
  - 29 (70%) AML with myelodysplasia-related changes
  - 4 (10%) therapy-related AML
  - 4 (10%) AML, NOS
  - 2 (5%) AML with inv(3)
  - 1 AML with t(6;9)
  - 1 AML with mutated NPM1
Myeloid proliferations related to Down syndrome

- Transient abnormal myelopoiesis
- Myeloid leukemia associated with Down syndrome
Myeloid Neoplasms with Germline Predispositions

• Myeloid neoplasms with germline predisposition without a pre-existing disorder or organ dysfunction
  – AML with germline *CEBPA* mutation
  – Myeloid neoplasms with germline *DDX41* mutation*

• Myeloid neoplasms with germline predisposition and pre-existing platelet disorders
  – Myeloid neoplasms with germline *RUNX1* mutation*
  – Myeloid neoplasms with germline *ANKRD26* mutation*
  – Myeloid neoplasms with germline *ETV6* mutation*

• Myeloid neoplasms with germline predisposition and other organ dysfunction
  – Myeloid neoplasms with germline *GATA2* mutation
  – Myeloid neoplasms associated with bone marrow failure syndromes
  – Myeloid neoplasms associated with telomere biology disorders
  – Juvenile myelomonocytic leukemia associated with neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders
  – Myeloid neoplasms associated with Down syndrome*

Overlap Between AML and MDS

• Unique MDS types
  – Ring sideroblasts
  – *SF3B1* mutations, isolated 5q deletions

• AML/MDS overlaps
  – Multilineage dysplasia or erythroid predominance
  – Complex karyotype
  – *ASXL1, TP53, U2AF1* mutations

• Unique AML types
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Summary

- Disease entities are not entirely defined by blast cell counts
- Common genetic changes may define new disease groups that may respond to targeted therapies
- Morphology continues to provide clues to common features between AML and MDS
Thank you for your attention