Myelodysplastic Syndromes

Lymphoma Tumor Board
Friday, September 16, 2016
Background

- Myelodysplastic syndrome (MDS): heterogeneous collection of bone marrow disorders characterized by:
  - dysplasia in bone marrow and blood cells
  - ineffective hematopoiesis
  - cytopenias
  - a tendency to develop acute myeloid leukemia
- Mean age at onset: 68 years
- Associated in some cases with environmental exposures such as to ionizing radiation or hydrocarbons such as benzene
- “Secondary” or therapy-related MDS can occur as a late sequela to previous treatment with genotoxic agents
- Aplastic anemia and Fanconi anemia can evolve into MDS
- Etiology: mutation[s] in multipotential bone marrow stem cells
- Classification system recently updated by the WHO in 2016: “WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues”
Revised 2016 WHO Classification System

- Intended to incorporate new knowledge of these disorders
- Revisions were influenced by the following:
  - “The discovery of recently identified molecular features has yielded new perspectives regarding diagnostic and prognostic markers that provide novel insights for the understanding of the pathobiology of these disorders.”
  - “Improved characterization and standardization of morphological features aiding in the differentiation of disease groups, particularly of the BCR-ABL1− myeloproliferative neoplasms (MPNs), has increased the reliability and reproducibility of diagnoses.”
  - “A number of clinical-pathological studies have now validated the WHO postulate of an integrated approach that includes hematologic, morphologic, cytogenetic, and molecular genetic findings.”
Revised 2016 WHO Classification System for MDS

- Terminology has changed to remove terms such as “refractory anemia” and “refractory cytopenia”
- New modifiers are: single vs. multilineage dysplasia, ring sideroblasts, excess blasts, or the del(5q) cytogenetic abnormality
- No changes to childhood MDS
- Biggest challenge is separating MDS from reactive causes of cytopenia and dysplasia
- Threshold to define dysplasia remains as 10% dysplastic cells in any hematopoietic lineage
- Myeloblast percentage determined by BM aspirate smears or touch preps remains critical in WHO MDS categories

Revised 2016 WHO Classification of MDS

<table>
<thead>
<tr>
<th>Name</th>
<th>Dysplastic lineages</th>
<th>Cytopenias*</th>
<th>Ring sideroblasts as % of marrow erythroid elements</th>
<th>BM and PB blasts</th>
<th>Cytogenetics by conventional karyotype analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with single lineage dysplasia (MDS-SLD)</td>
<td>1</td>
<td>1 or 2</td>
<td>&lt;15%/&lt;5%†</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any, unless fulfills all criteria for MDS with isolated del(5q)</td>
</tr>
<tr>
<td>MDS with multilineage dysplasia (MDS-MLD)</td>
<td>2 or 3</td>
<td>1-3</td>
<td>&lt;15%/&lt;5%†</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any, unless fulfills all criteria for MDS with isolated del(5q)</td>
</tr>
<tr>
<td>MDS with ring sideroblasts (MDS-RS)</td>
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</tr>
<tr>
<td>MDS-RS with single lineage dysplasia (MDS-RS-SLD)</td>
<td>1</td>
<td>1 or 2</td>
<td>≥15%/&lt;5%†</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any, unless fulfills all criteria for MDS with isolated del(5q)</td>
</tr>
<tr>
<td>MDS-RS with multilineage dysplasia (MDS-RS-MLD)</td>
<td>2 or 3</td>
<td>1-3</td>
<td>≥15%/&lt;5%†</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any, unless fulfills all criteria for MDS with isolated del(5q)</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>1-3</td>
<td>1-2</td>
<td>None or any</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>del(5q) alone or with 1 additional abnormality except -7 or del (7q)</td>
</tr>
<tr>
<td>MDS with excess blasts (MDS-EB)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS-EB-1</td>
<td>0-3</td>
<td>1-3</td>
<td>None or any</td>
<td>BM 5%-9% or PB 2%-4%, no Auer rods</td>
<td>Any</td>
</tr>
<tr>
<td>MDS-EB-2</td>
<td>0-3</td>
<td>1-3</td>
<td>None or any</td>
<td>BM 10%-19% or PB 5%-19% or Auer rods</td>
<td>Any</td>
</tr>
<tr>
<td>MDS, unclassifiable (MDS-U)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with 1% blood blasts</td>
<td>1-3</td>
<td>1-3</td>
<td>None or any</td>
<td>BM &lt;5%, PB = 1%,‡ no Auer rods</td>
<td>Any</td>
</tr>
<tr>
<td>with single lineage dysplasia and pancytopenia</td>
<td>1</td>
<td>3</td>
<td>None or any</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any</td>
</tr>
<tr>
<td>based on defining cytogenetic abnormality</td>
<td>0</td>
<td>1-3</td>
<td>&lt;15%§</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>MDS-defining abnormality</td>
</tr>
<tr>
<td>Refractory cytopenia of childhood</td>
<td>1-3</td>
<td>1-3</td>
<td>None or any</td>
<td>BM &lt;5%, PB &lt;2%</td>
<td>Any</td>
</tr>
</tbody>
</table>

* Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, <100 x 10^9/L; and absolute neutrophil count, <1.8 x 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be <1 x 10^9/L.
† If SF3B1 mutation is present.
‡ One percent PB blasts must be recorded on at least 2 separate occasions.
§ Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.
“Refractory anemia with ringed sideroblasts (RARS). Bone marrow aspirate smear (Wright-Giemsa stain). The two panels in this slide illustrate that the megakaryocytes and the granulocytes show normal morphology. The erythroid precursors in this slide do show some mild nuclear/cytoplasmic dyssynchrony (arrow).”
“Refractory cytopenia with multilineage dysplasia (RCMD). Cytogenetic preparation. The karyotype performed from bone marrow cells was: 46, XY [80%] 46, XY, del (5q)(q11q33), del (7q) (q11q36) [20%].”
“Refractory cytopenia with multilineage dysplasia (RCMD). Bone marrow biopsy (H & E stain). The biopsy demonstrates erythroid hyperplasia. Immature erythroid precursors (arrows) have round to oval vesicular nuclei, a prominent, comma-shaped nucleolus that often is close to the nuclear membrane, and a rim of amphophilic cytoplasm. Erythroid precursors that are more mature (double arrows) have homogenous, darkly-stained nuclei.”
Age and Sex in MDS

- Overall incidence in this analysis: 3.4 per 100,000

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*P for trend < .05

Rollison DE et al Blood 2008;112:45-52.

Slide borrowed from Dr. David Steensma
MDS cytogenetic scoring system

<table>
<thead>
<tr>
<th>Prognostic subgroups, % of patients</th>
<th>Cytogenetic abnormalities</th>
<th>Median survival, y</th>
<th>Median AML evolution, 25% y</th>
<th>Hazard ratios OS/AML</th>
<th>Hazard ratios OS/AML†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good (4%* / 3%†)</td>
<td>−Y, del(11q)</td>
<td>5.4</td>
<td>NR</td>
<td>0.7/0.4</td>
<td>0.5/0.5</td>
</tr>
<tr>
<td>Good (72%* / 66%†)</td>
<td>Normal, del(5q), del(12p), del(20q), double including del(5q)</td>
<td>4.8</td>
<td>9.4</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Intermediate (13%* / 19%†)</td>
<td>del(7q), +8, +19, i(17q), any other single or double independent clones</td>
<td>2.7</td>
<td>2.5</td>
<td>1.5/1.8</td>
<td>1.6/2.2</td>
</tr>
<tr>
<td>Poor (4%* / 5%†)</td>
<td>−7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex: 3 abnormalities</td>
<td>1.5</td>
<td>1.7</td>
<td>2.3/2.3</td>
<td>2.6/3.4</td>
</tr>
<tr>
<td>Very poor (7%* / 7%†)</td>
<td>Complex: &gt; 3 abnormalities</td>
<td>0.7</td>
<td>0.7</td>
<td>3.8/3.6</td>
<td>4.2/4.9</td>
</tr>
</tbody>
</table>

OS indicates overall survival; and NR, not reached.

* Data from patients in this IWG–PM database, multivariate analysis (n = 7012).
† Data from Schanz et al8 (n = 2754).

Peter L. Greenberg et al. Blood 2012;120:2454-2465
### IPSS-R Prognostic Score Values

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very good</td>
<td>—</td>
<td>Good</td>
<td>—</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very poor</td>
</tr>
<tr>
<td>BM blast, %</td>
<td>≤ 2</td>
<td>—</td>
<td>&gt; 2%–&lt; 5%</td>
<td>—</td>
<td>5%–10%</td>
<td>&gt; 10%</td>
<td>—</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥ 10</td>
<td>—</td>
<td>8–&lt; 10</td>
<td>&lt; 8</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ 100</td>
<td>50–&lt; 100</td>
<td>&lt; 50</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ANC</td>
<td>≥ 0.8</td>
<td>&lt; 0.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

— indicates not applicable.

Peter L. Greenberg et al. *Blood* 2012;120:2454-2465
Survival stratified by marrow blast subgroup

Peter L. Greenberg et al. Blood 2012;120:2454-2465
Survival based on IPSS-R prognostic risk-based category

Peter L. Greenberg et al. *Blood* 2012;120:2454-2465

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IWG-PM patients marrow blast subgroups: Impact on AML evolution

Peter L. Greenberg et al. *Blood* 2012;120:2454-2465
Survival stratified by patient age (> 60 years vs. ≤ 60 years) and IPSS-R prognostic category

Peter L. Greenberg et al. *Blood* 2012;120:2454-2465
Age-adjusted IPSS-R risk categories

Peter L. Greenberg et al. Blood 2012;120:2454-2465
Comparison of IPSS-R and IPSS subgroups within the IWG-PM database patient cohort

Peter L. Greenberg et al. Blood 2012;120:2454-2465
Genomic architecture of MDS

Frequency of driver mutations identified in the sequencing screen or by cytogenetics in a cohort of 738 patients, broken down by MDS subtype

Oncogenic mutations identified in MDS

Clonal and subclonal driver mutations in MDS


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Outcome by clonal or subclonal driver mutations

Relationship between # of oncogenic mutations & outcome

A

Leukemia-free survival

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)

p < 0.0001

Time (months)

B

Incidence of AML transformation

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)

p < 0.0001

Time (months)

C

Leukemia-free survival

Not mutated (n=514)
Variant not known to be oncogenic (n=7)
Known oncogenic mutation (n=74)

p = 0.03
p = 0.001

Time (months)


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Predicting leukemia-free survival

Therapeutic Approach to MDS

- The IPSS scoring system can help guide patients for more aggressive treatment and can help determine the best timing of this therapy.

- Supportive care with blood product support and hematopoietic growth factors (e.g. erythropoietin) is the main type of therapy.

- Three agents have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDS:
  - 5-azacytidine: 21-month median survival
  - Decitabine: Complete response rate reported as high as 43%
  - Lenalidomide: Effective in reducing red blood cell transfusion requirement in patients with the chromosome 5q ("5q-") deletion subtype of MDS
Therapeutic Approach to MDS

Establish Diagnosis and Prognosis
a.) CBC
b.) Marrow Blasts; iron stain
c.) Cytogenetics
d.) transfusional history

is treatment needed?
  No → Observe
  Yes →

  is 5q minus present?
  Yes → Lenalidomide
  No →

  Is patient immunosuppression candidate?
  Yes → ATG
  No →

  Is pt. transplant candidate now?
  Yes → (Based on age, PS, co-morbidities, MDS prognosis) proceed to either full or RIC allotx but consider reducing blast count with DNAMTI
  No →

  Selected lower risk patients
  No → Lenalidomide

Use DNAMTI
Survival after Allogeneic Transplants for Myelodysplastic Syndrome (MDS), 2003-2013

By Disease Status for HLA Match Sibling

- Early (n=960)
- Advanced (n=1,626)

p=0.003
Survival after Allogeneic Transplants for Myelodysplastic Syndrome (MDS), 2003-2013

Probability, %

Years

By Disease Status for Unrelated Donor

p<0.001

Early (n=1,442)

Advanced (n=2,433)
Survival after HLA Match Sibling Donor Transplants for Myeloproliferative Diseases, 2003-2013

Probability, %

Years

Myelofibrosis (n=596)

Other MPD (n=688)

p=0.092

By Disease
References


- [http://imagebank.hematology.org/](http://imagebank.hematology.org/)

- [https://www.cibmtr.org/pages/index.aspx](https://www.cibmtr.org/pages/index.aspx)