High-risk MDS and clinical trials

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MDS risk stratification and prognostic factors

• Give healthcare providers & patients and their families insights into what to expect
  • Based upon what happened to those with similar MDS features before them
  • As therapies change, prognosis changes

• Relevant to determine eligibility for available treatments
  • Depends on the therapy

• Individualize prognosis, and possibly therapy whenever possible
  • Determining timing & selection for therapy
    • e.g. transfusion & red cell growth factors vs. chemotherapy or even allogeneic transplantation
  • Clinical Trial eligibility
MDS prognostic factors

- Better blood counts are good
- Not needing transfusions is good
- Lower blasts are good
- Having no cytogenetic abnormalities is good
- Younger age is good
- Being able to function better is good
Other prognostic factors

- Therapy-related: prior chemotherapy or radiation therapy
- Albumin
- Ferritin (iron stores)
- Presence of blood blasts
- Age, general health, performance status
- Bone marrow fibrosis
- Many others
Risk Assessment

Newly Diagnosed MDS

Risk Model

Lower-risk disease

- Decrease transfusion burden
- Decrease symptoms
- Improve quality of life

Higher-risk disease

- Alter natural history of disease
- Prevent progression to acute myeloid leukemia
- Improve overall survival
# International Prognostic Scoring System

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM blasts (%)</td>
<td>&lt;5</td>
<td>5-10</td>
<td>--</td>
<td>11-20</td>
<td>21-30</td>
</tr>
<tr>
<td>Chromosomes*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low blood counts</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Good: nl, -y, del(5q), del(20q) Int: all others
Poor: complex or chromosome 7 abn

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low: 0</td>
<td></td>
</tr>
<tr>
<td>Intermediate-1: 0.5-1</td>
<td></td>
</tr>
<tr>
<td>Intermediate-2: 1.5-2</td>
<td></td>
</tr>
<tr>
<td>High: ≥ 2.5</td>
<td></td>
</tr>
</tbody>
</table>

Greenberg P et al, Blood 1997; 89:2079-88
## Revised IPSS

<table>
<thead>
<tr>
<th>Prognostic Subgroup</th>
<th>Cytogenetic Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Good</td>
<td>-Y, del(11q)</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(5q), del(12p), del(20q), double including del(5q)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>del(7q), +8, +19, i(17q), any other single or double independent clones</td>
</tr>
<tr>
<td>Poor</td>
<td>-7, inv(3)/t(3q)/del(3q), double including-7/ del(7q), complex: 3 abnormalities</td>
</tr>
<tr>
<td>Very Poor</td>
<td>Complex: &gt; 3 abnormalities</td>
</tr>
</tbody>
</table>

<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>Chromosomes</td>
<td>Very good</td>
<td>--</td>
<td>Good</td>
<td>--</td>
<td>Int</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, g/dL</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, K/µL</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, K/µL</td>
<td>≥ 0.8</td>
<td>&lt; 0.8</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Greenberg P. Blood 2012;120: 2454-2465
## Revised IPSS

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>≤ 1.5</td>
</tr>
<tr>
<td>Low</td>
<td>&gt; 1.5 – 3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt; 3 – 4.5</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 4.5 – 6</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt; 6</td>
</tr>
</tbody>
</table>

[Greenberg P. Blood 2012;120: 2454-2465](#)
You can, for example, never foretell what any one man will do, but you can say with precision what an average number will be up to. Individuals vary, but percentages remain constant. So says the statistician.” - Sherlock Holmes 1890 [Sir Arthur Conan Doyle: The Sign of Four, Chapter 10, p.137]
Heterogeneity in Outcomes in MDS

Survival

Very Low  Low  Intermediate  High  Very High

IPSS-R

Dead  Alive

Nazha A, et al. ASH 2018
Cancer Genomics

Mutation discovery / Clonality Patient care

- Cytogenetics
- Candidate gene sequencing
- Whole Genome Sequencing

• diagnosis
• risk stratification
• therapy

( unbiased comprehensive platform)
>90% of patients with MDS have at least 1 mutation

Molecular Mutations in MDS

- Splicing Factors (~50%)
  - SF3B1 (18%)
  - U2AF1 (12%)
  - SRSF2 (12%)
  - ZRSR2 (5%)
  - Others (5%)
  Rarely co-occur with each other

- Both Splicing Factors (SF) & Epigenetic Regulators (ER)
  - Overlap (25%)

- Epigenetic Regulators (~45%)
  - TET2 (20%)
  - ASXL1 (15%)
  - DNMT3A (12%)
  - EZH2 (5%)
  - IDH1/2 (5%)
  - Others (5%)
  Often co-occur except for TET2 and IDH

- TP53 and no SF or ER (~5%)
  Often complex karyotypes with frequent del(5q), abnormal chromosome 7, and monosomies

- No Common Abnormality (~5%)

- Karyotype Abnormality Only (~5%)

- Mutations in Other Genes Only (~15%)
  - Transcription Factors
    - RUNX1, ETV6, PHF6, GATA2, ...
  - Kinase Signalling
    - NRAS, KRAS, JAK2, CBL, ...
  - Cohesins
    - STAG2, SMC3, RAD21, ...
  - DNA Repair

Bejar R and Steensma D, Blood 2014
From Papaemmanuil et al, Blood 2013.
IPSS and TP53, EZH2, ETV6, RUNX1 and ASXL1 mutations

From Bejar et al, NEJM 2011.
Treatments for high-risk MDS

• Decitabine
• Azacitidine
• Intensive Chemotherapy
• Stem-cell transplant
• Clinical trials
Gene hypermethylation in MDS

Expressed (or ready for expression)

Silenced

Adapted from Issa, JP
Hypomethylating cytosine analogs

Cytosine  5-methyl-cytosine  Azacytidine  Decitabine

First randomized study of azacitidine in patients with MDS

75 mg/m$^2$/d SC x 7 days every 4 weeks

Responses (after 4 cycles)

Complete remission - 7%
Partial remission - 16%
Improved - 37%
Total - 60%

Azacitidine survival study in higher-risk MDS

Screening/Central Pathology

Review

Investigator CCR

Treatment Selection

Randomization

CCR (Conventional Care Regimen)

- Best supportive care only
- Low-dose Ara-C
- Standard chemotherapy (7 + 3)

AZA 75 mg/m²/d x 7 d q28 d

Overall Survival in higher-risk: Azacitidine vs CCR

Azacitidine treatment

• Subcutaneous or intravenous injections daily for 7 [or 5(+2)] days every 28 days
• Median cycles to first response: 2-3
• Response may require 4-6 cycles
• Do NOT need a complete response for benefit
• Responders need to continue treatment to sustain response.
Decitabine- ADOPT study

• Decitabine 20 mg/m2 IV daily x for 5 days; 28-day cycles
• Overall response rate 32% (17% complete remission and 15% marrow complete remission)
• Overall improvement rate 51%, including 18% improvement in blood counts.
• Similar response rates in all risk categories.
• 82% of patients who improved showed responses by the end of cycle two.
• Survival advantage not yet demonstrated for decitabine, likely due to inferior study designs.

Decitabine after Azacitidine may help some patients

Table II. Response summary.

<table>
<thead>
<tr>
<th>Responses</th>
<th>Number (percent)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>3 (21)</td>
<td></td>
</tr>
<tr>
<td>Marrow CR with HI</td>
<td>1 (7)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (36)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease/death</td>
<td>4/1 (29/7)</td>
<td></td>
</tr>
<tr>
<td>Number of DAC courses to response</td>
<td>3 (1–5)</td>
<td></td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>6 (1–14.8)</td>
<td></td>
</tr>
</tbody>
</table>

CR, complete remission; HI, hematological improvement; DAC, decitabine.

Figure 1. Overall survival of all the 14 patients.

Table III. Characteristics of responders.

<table>
<thead>
<tr>
<th>Number of prior Aza courses</th>
<th>Best response to Aza</th>
<th>Reason off Aza/weeks off Aza</th>
<th>Weeks from prior Aza before DAC</th>
<th>Best response to DAC/courses to response</th>
<th>Response duration (months)</th>
<th>Percent marrow blasts pre/at response</th>
<th>Platelets pre/at response</th>
<th>ANC pre/at response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>Marrow CR</td>
<td>PD</td>
<td>CR/3</td>
<td>9.7</td>
<td>15/1</td>
<td>24/336</td>
<td>1.1/3.2</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>SD</td>
<td>NR</td>
<td>Marrow CR/3</td>
<td>8.2</td>
<td>8/4</td>
<td>65/95</td>
<td>1.8/5.1</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>SD</td>
<td>NR</td>
<td>CR/5</td>
<td>11.3+</td>
<td>12/3</td>
<td>80/234</td>
<td>0.6–1.4</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>N/A</td>
<td>Toxicity</td>
<td>CR/1</td>
<td>10.2</td>
<td>13/4</td>
<td>24/110</td>
<td>0.38/2.8</td>
</tr>
</tbody>
</table>

CR, complete remission; Aza, azacitidine; DAC, decitabine; SD, stable disease; PD, progressive disease; NR, no response; ANC, absolute neutrophil count.

Decitabine 20mg/m2 IV days 1-5 on a 28-day cycle
Azacitidine vs. Decitabine
Outcomes after failure of treatment

- IPSS-R best predicts outcomes
- SD after 6 mo unlikely to improve -> clinical trials

2014 ASH Abstracts:
3275 (Nazha et al.): IPSS-R best predicts outcomes
3273 (Nazha et al.): SD after 6 mo unlikely to improve -> clinical trials

<table>
<thead>
<tr>
<th>Type of salvage</th>
<th>N</th>
<th>ORR</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>165</td>
<td>NA</td>
<td>3.6</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>122</td>
<td>NA</td>
<td>4.1</td>
</tr>
<tr>
<td>Low-dose chemotherapy</td>
<td>32</td>
<td>0/18</td>
<td>7.3</td>
</tr>
<tr>
<td>Intensive chemotherapy</td>
<td>35</td>
<td>3/22</td>
<td>8.9*</td>
</tr>
<tr>
<td>Investigational therapy</td>
<td>44</td>
<td>4/36</td>
<td>13.2*†</td>
</tr>
<tr>
<td>Allogeneic transplantation</td>
<td>37</td>
<td>13/19</td>
<td>19.5*†</td>
</tr>
</tbody>
</table>

Prébet et al. JCO 2011.
Intensive chemotherapy

Consider in:
- Younger fit patients <65-70
- High blast percentage (>10%)
- Non-adverse cytogenetics
- Transplant candidate with donor
- Post-remission chemotherapy should be given

CR 40-60%, median duration CR <1yr
Early mortality 17%, 5yr OS 8%
Pearls - 1

- Occurs more often in older patients with co-morbidities
  - Require more holistic medical care
- Common supportive care requirements
  - Effects of low blood counts (anemia, risk of bleeding or infection)
  - Coordination of blood product support, monitoring, antibiotics
- Treatments are prolonged
  - Effects of disease frequently worsen in early stages of therapy
    - i.e. “1 step backward before 2 steps forward”
  - Requires close coordination with MD, APP, RN, SW care team
- Balance of disease intervention while focusing on QoL
Pearls - 2

• More difficult, more symptomatic, or more advanced MDS

• Consider azacitidine or decitabine
  • ‘Low intensity’ chemotherapy given 5 or 7 consecutive days, every 4 weeks indefinitely
    • Do not work for everyone, or forever
    • Consider clinical trial of novel agent

• Evaluation in BMT program

• Supportive care (transfusions & antibiotics, etc.)

• Treatment of resistant MDS is very difficult
Pearls - 3

• Important to set expectations and goals as not all patients experience a major improvement

• Improvements in CBC
  • Decrease frequency or independence from transfusions

• Improved, or Maintained Quality of Life
  • Stronger, stamina, independent

• Continue therapy ‘long-term’ to maintain benefit & stability

• Sometimes success is ‘stability’, or not worsening of MDS

• Hard to cure – goal is often maintain control
Pearls - 4

• Almost all patients benefit from therapy
  • Depends on scenario and patients needs
  • Set individual patient goals

• Current treatments still not adequate for many
  • We must work together to advance MDS treatments and outcomes
    • Clinical trials
      • Molecularly-targeted therapy
Essentials for MDS patients

• Know your IPSS-R risk group
• Know your treatment options
  – Including transplant, clinical trials
• Know what your treatment goals are
• Know the potential side effects of your treatments
• Know available MDS resources
• Have a caregiver available/involved
• Knowledge = Power

• Take ownership of your care

• Do you have a framework for approaching a new cancer diagnosis?
• Disease specifics (micro-level)
  • exact subtype of leukemia / MDS
  • genetic information of MDS

• Disease specifics (macro-level)
  • Risk-stratification
• Prognosis
  • is it curable?
  • chance of remission
  • overall survival

• Treatment
  • Primary treatment
    • Chemotherapy, stem-cell transplant
  • Phases of treatment
    • Continuous treatment?
    • Induction, consolidation, maintenance?
  • Supportive care
NCCN Guidelines® & Clinical Resources

NCCN Guidelines®

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- NCCN Guidelines for Treatment of Cancer by Site
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- NCCN Guidelines for Supportive Care
- NCCN Guidelines for Specific Populations
- NCCN Guidelines for Patients

The NCCN guidelines are FREE! Register for a free account, then click on the cancer types below to display a drop-down of options. If you are still having an issue, please contact us.

NCCN GUIDELINES FOR TREATMENT OF CANCER BY SITE

- Acute Lymphoblastic Leukemia (Adult and AYA)
- Acute Lymphoblastic Leukemia (Pediatric and AYA)
- Acute Myeloid Leukemia
- AIDS-Related Kaposi Sarcoma
NCCN Member Institutions

Click on any of the network locations to get more information about the cancer center and to find links to the NCCN Member Institution’s web site.
NCCN Guidelines Version 1.2020
Myelodysplastic Syndromes
NCCN Evidence Blocks™

EVALUATION OF RELATED ANEMIA

- H&P
- CBC, platelets, differential, reticulocyte count
- Examination of peripheral smear
- Bone marrow aspiration with iron stain + biopsy + cytogenetics
- Serum EPO level
- Rule out coexisting causes

TREATMENT OF SYMPTOMATIC ANEMIA

<table>
<thead>
<tr>
<th>Serum EPO ≤500 mU/mL</th>
<th>Ring sideroblasts &gt;15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Treat coexisting causes</td>
<td></td>
</tr>
<tr>
<td>- Replace iron, folate, B₁₂ if needed</td>
<td></td>
</tr>
<tr>
<td>- RBC transfusions (CMV-safe)</td>
<td></td>
</tr>
<tr>
<td>- Supportive care</td>
<td></td>
</tr>
</tbody>
</table>

| Serum EPO 40,000-60,000 U 1-2 x/wk subcutaneous |
| Darbepoetin alfa 150-300 mcg every other wk subcutaneous |

- Continue EPO or darbepoetin, decrease dose to tolerance
- Continue lenalidomide, decrease dose to tolerance

FOLLOW-UP

- Response
- No response
- See (MDS-4)

- Response
- No response (despite adequate iron stores)
- See (MDS-4)

Response
- Continue EPO or darbepoetin, consider adding lenalidomide or G-CSF 1-2 mcg/kg x/wk subcutaneous

See Evidence Blocks for Initial Treatment on MDS-5A
See Evidence Blocks for Subsequent Treatment on MDS-5B

See Supportive Care (MDS-7)

2nd Regional Symposium on Myelodysplastic Syndromes
5-6 March 2020, Tel Aviv, Israel

Tel Aviv 2020
Clinical trials

- Frontline
- Relapsed / Refractory setting
The **MEDALIST** Trial: Results of a Phase 3, RPCC Study of Luspatercept to Treat Patients with Very Low-, Low-, or Intermediate-Risk MDS Associated Anemia with Ring Sideroblasts Who Require RBC Transfusions

- **153 Patients** Luspatercept 1mg/kg SC every 21 days
  - 38% achieved transfusion-independence at 8 weeks
  - 28% achieved transfusion-independence at 12 weeks

- **76 Patients** Placebo
  - 13% achieved transfusion-independence at 8 weeks
  - 8% achieved transfusion-independence at 8 weeks
Imetelstat Treatment Leads to Durable Transfusion Independence in RBC Transfusion-Dependent, Non-Del(5q) Lower Risk MDS Relapsed/Refractory to ESA

- 38 Patients received Imetelstat 7.5 mg/kg IV every 4 weeks
  - 37% achieved transfusion-independence at 8 weeks
  - 26% achieved transfusion-independence at 24 weeks
  - Median time to onset of TI 8 weeks
  - Median duration of TI not reached

  - Neutropenia and thrombocytopenia in 20-25%
Guadecitabine (SGI110) in MDS

Phase I: Less rapid degradation by cytidine deaminase = longer half life than decitabine

Phase II: n=102, 60mg/m2 or 90mg/m2

• Previously treated patients:
  – 30% ORR

• Treatment naive patients: 20% CR
  – 58% transfusion-independent for RBC
  – 46% transfusion-independent for platelets
Is Immune Exhaustion an Issue in MDS?

**Diagram:**
- **Left Panel:** PD-L1/PD-1 binding inhibits T cell killing of tumor cell.
  - Tumor cell
  - PD-L1
  - Antigen
  - T cell receptor
  - PD-1
  - T cell

- **Right Panel:** Blocking PD-L1 or PD-1 allows T cell killing of tumor cell.
  - Tumor cell death
  - PD-L1
  - Anti PD-L1
  - Anti PD-1
  - PD-1
  - T cell

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Trials Using Immune Checkpoint Inhibitors?

- Phase II: Azacitidine + Nivolumab or Ipilimumab (MDA)
  - ORR 60-70% as FRONTLINE treatment
  - CR 40% with AZA + Nivolumab, 14% with AZA + IPI
  - CR 6/20 IPI alone (30%)

- Phase Ib: AZA + Atezolizumab
  - ORR 62%
  - CR 14%
New drugs and targets

- NTX-301
- ASTX-727 LD
- GSK3326595
- SEA-CD70
- APR-246
- Anti-CD47 Antibody Magrolimab (5F9)
- Pevonidistat
- Rigosertib
The nitrogen in our DNA, the calcium in our teeth, the iron in our blood, the carbon in our apple pies were made in the interiors of collapsing stars. We are made of star stuff.
– Carl Sagan
It is something that is called MDS. It is a rare blood disorder that affects the bone marrow. I'm going to beat this. My doctors say it and my faith says it.

-Robin Roberts
Pankit Vachhani, MD

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205-975-7850 (office)