Myelodysplastic Syndromes (MDS)

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First: What are MDS?

Four defining features of MDS

1) Marrow failure -> symptoms (low blood counts (=cytopenias) – anemia is most common)
2) Clonal disorders (abnormal chromosomes/karyotype; acquired DNA mutations)
3) Characteristic “dysplastic” blood and marrow cell appearance (i.e., abnormally formed cells)
4) Instability / tendency to progress to acute myeloid leukemia – formerly “preleukemia”

Age-dependent nature of MDS (US)

- Overall incidence in this analysis: 3.4 per 100,000
- SEER registry: ~13,000 new US cases per year
- Claims-based data: >30,000 US cases per year

How do MDS originate?

DNA replication error rate:
~1 error in 10^8 base pairs (100 million)
But 99% of the errors are corrected...
So, net: ~1 in 10^10 base pairs (1 billion)
Each cell has 3 x 10^9 base pairs (3 billion)
So ~3 in 3 chance of an error with each cell division
But most (~99%) errors are meaningless

What about MDS after chemotherapy or radiation for another disease? (i.e., “therapy-related” or “t-MDS”)

Diverse bone marrow stem cells
A pre-existing TP53 mutant cell exists in some people
TP53 mutant cells survive stress better
TP53 mutant cells come to dominate; Some have acquired additional mutations
MDS risk stratification: Revised International Prognostic Scoring System (IPSS-R)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Categories and Associated Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic risk group</td>
<td>Very good</td>
</tr>
<tr>
<td>Marrow blast proportion</td>
<td>0</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≤10 g/dL</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>≤0.8 x 10⁹/L</td>
</tr>
<tr>
<td>Platelet count</td>
<td>≤150 x 10⁹/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Points</th>
<th>% patients</th>
<th>Median survival, years</th>
<th>Median survival for pts under 60 years</th>
<th>Time until 25% of patients develop AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>0-1.5</td>
<td>19%</td>
<td>8.8</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Low</td>
<td>2.0-3.0</td>
<td>38%</td>
<td>5.3</td>
<td>8.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3.5-4.5</td>
<td>20%</td>
<td>3.8</td>
<td>5.2</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>5.0-6.0</td>
<td>13%</td>
<td>1.5</td>
<td>2.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;6.0</td>
<td>10%</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>


Why Has Therapy of MDS Been So Challenging?

Unlike leukemia, there are no widely useful MDS “cell lines”. Several animal models now exist, but may not be representative. This makes screening targeted agents more challenging.

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

Challenge #1 to narrowly targeted therapies
- Genetically modified mouse for disease modeling
- Genomic architecture of MDS
  - Frequency of driver mutations identified in the sequencing screen or by cytogenetics in the cohort of 738 patients, broken down by MDS subtype.

Challenge #2 to developing narrowly targeted therapies
- Long “tail” of lesions present at <2% level

Images from medieval Bestiarum Vocabulum

How can MDS be treated?

Goals of Care in MDS
Transfusion principles

- **Whole blood** is separated into red blood cells (RBCs), platelets, and plasma

- **Red cells**: typical volume is 250 mL (a half pint)
  - 1 Unit raises hemoglobin ~1 g/dL, hematocrit ~3%
  - Typically given for hemoglobin <8 g/dl or symptoms, hematocrit <24%
  - Common reactions include fevers, fluid overload, hives; infections very rare today
  - Irradiated if patient may be transplanted; leukoreduced for all
  - Special types: HLA matched, washed

- **Platelets**: typical volume is ~300 mL (6 pooled units or 1 apheresis/single-donor unit)
  - Typically given for platelet count <10 x 10^9/L; raises by variable amount (average 30)
  - Level needs to be 30 x 10^9/L for mildly invasive procedures, 50 x 10^9/L for most surgeries/lumbar puncture, 100 x 10^9/L for neurosurgery
  - Common reactions include fevers, hives
  - Patients can become “immune” (alloimmunized) with time

- **White cells** (granulocytes) can’t be transfused except under very special circumstances

How does the marrow make red cells?

- EPO = erythropoietin
- Products in the US: epoetin alfa (Procrit), darbepoetin alfa (Aranesp)

“Who is likely to respond to Erythropoiesis Stimulating Agents (ESAs) in MDS?”

<table>
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<tr>
<th>Total Score (from below)</th>
<th>IWWG 2000 erythroid response rate (patients)</th>
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<tbody>
<tr>
<td><strong>High likelihood of response</strong>: &gt; +1</td>
<td>74% (n=34)</td>
</tr>
<tr>
<td><strong>Intermediate likelihood</strong>: -1 to +1</td>
<td>23% (n=31)</td>
</tr>
<tr>
<td><strong>Low likelihood of response</strong>: &lt;-1</td>
<td>7% (n=39)</td>
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<tr>
<th>Serum EPO level (U/L)</th>
<th>RBC transfusion requirement</th>
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<tr>
<td>&lt;100</td>
<td>+2 pts ≥2 Units/month +2 pts</td>
</tr>
<tr>
<td>100-500</td>
<td>+1 pt ≥2 Units/month -2 pts</td>
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<tr>
<td>&gt;500</td>
<td>-3 pts</td>
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International Working Group (IWG) 2000 Erythroid Response Criterion: >1.5 g/dL Hb increment, or transfusion independence
Available iron chelators

- **Deferasirox**
- **Deferoxamine**
- **Deferiprone** – not approved for MDS in US
- **Wheatgrass** – unapproved supplement

**What about platelet growth factors? (“Thrombopoiesis stimulating agents”)**

- **Goal:** reduce need for platelet transfusions and “clinically significant bleeding events”
- Moderately successful in MDS
- **Not FDA approved for MDS**
  - Approved for other conditions
  - Early studies raised concern about blast growth stimulation
  - More recent analyses suggest only modest effect

**Why don’t we use white cell growth factors commonly in MDS?**

- **Cost**
- Never been shown to improve survival
- Very modest benefit
  - Neutrophil dysfunction
- Side effects (e.g., bone pain, fevers, spleen rupture, leukemoid reaction)
- Some blasts may use as a growth factor

**Lenalidomide in MDS**

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<td>Transfusion Independence</td>
<td>67%</td>
<td>56%</td>
<td>26%</td>
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<td>Complete Cytogenetic Response</td>
<td>45%</td>
<td>29%</td>
<td>9%</td>
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<td>Median Response Duration</td>
<td>&gt; 2 years</td>
<td>83 weeks</td>
<td>41 weeks</td>
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*del(5q)* is the strongest genetic predictor of response for MDS
TP53 mutations are markers of shorter survival/relapse

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**AZA-001 survival study (Higher risk MDS): Azacitidine vs “Conventional care”**

- Log-Rank, p=0.0001
- HR = 0.58 [95% CI: 0.43, 0.77]
- Deaths: Aza = 82, Control = 113
- Difference: 9.4 months
- 15 months
- 24.4 months

Control arm (supportive care or chemotherapy)

May be better to give 7 days than <7 days IV same as SC

Decitabine (D-0007) registration study outcomes

How do azacitidine or decitabine work? Unknown...

Outcomes after azacitidine or decitabine failure

Outcomes after failure

What Are The Greatest Needs In The MDS Field?

MDS clinical research priorities

Largest specific unmet therapeutic needs

- More accurate diagnostic methods
  - Current techniques are to some extent subjective
  - Molecular testing is helping in ambiguous cases
- Better prognostication
  - There are limits to this, but helps decide on therapy
- Better systems of health care delivery
  - In the US we use our health care dollars poorly / inefficiently
- Improved therapy

- Increase proportion of aza/decitabine responders
  - Current complete response rate 10-20%
  - Current overall response rate 40-50%
  - Average duration of response 8-11 months
  - Need to increase also depth of response and duration
- Treatments for patients after aza/decitabine stop working
- Treatments for “higher” lower risk patients
  - Defined by molecular genetics or other features
- Who else does lenalidomide work for besides people with del(5q)?
- Other curative therapies besides transplant

Comparison to decitabine failure: median survival 4.3 months, n=87


Navada SC et al / Clin Invest. 2014
What About Stem Cell Transplant?

What Is Coming Next?

Representative experimental therapies

- Luspatercept
  - Antibody given every 3 weeks; MEDALIST trial is 48 weeks vs placebo
- Imetelstat
  - Inhibitor of telomerase
- Oral azacitidine (CC-486), oral decitabine+deaminase inhibitor (cedazuridine/ASTX727)
- SGI-110/guadecitabine
- Venetoclax
  - Inhibitor of BCL-2; approved for CLL/lymphoma
- Immune checkpoint inhibitors (nivolumab, pembrolizumab, ipilimumab)
  - Approved for solid tumors; limited activity in MDS alone, but in combination?
- Chimeric antigen receptor (CAR-T) cells
  - Need to define ideal target (CD33? CD123?)

An approach to MDS

Predicting the future accurately is notoriously difficult. Where are our robot housekeepers, rocket trains, and flying cars?!
If I can help...

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