Myelodysplastic Syndromes: Disease Overview, New Therapies, and Treatment Options

Rafael Bejar MD, PhD
MDS Foundation
Patients & Caregivers LIVING with MDS Forums
February 3, 2018
Overview

• Introduction to MDS

• Clinical Practice
  - Making the diagnosis
  - Classification
  - Risk stratification

• Treatment Goals and Options

• Novel Therapies

• Questions and Answers
65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.
Myelodysplastic Syndromes

• Shared features:
  – Low blood counts
  – Clonal overgrowth of bone marrow cells
  – Risk of transformation to acute leukemia

• Afflicts 15,000 – 45,000 people annually

• Incidence rises with age (mean age 71)
MDS Incidence Rates 2000-2008

US SEER Cancer Registry Data

Incidence Rate per 100,000

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

*P for trend < .05
Etiology of MDS

- **<5%**
  - Familial or Congenital

- **10-15%**
  - Topoisomerase II inhibitors
  - Ionizing radiation
  - DNA alkylating agents

- **85%**
  - “De novo” (idiopathic, primary)

Often early onset and part of a larger syndrome
Peaks 1-3 or 5-7 years following exposure
Median age ~71 years; increased risk with aging

Slide adapted from Dr. David Steensma
Making the Diagnosis
Cytopenia(s):
- Low hemoglobin, or
- Low neutrophil count, or
- Low platelet count

MDS “decisive” criteria:
- >10% dysplastic cells in 1 or more lineages, or
- 5-19% blasts, or
- Abnormal karyotype typical for MDS, or
- Specific mutation typical of MDS

Other causes of cytopenias and morphological changes EXCLUDED:
- Vitamin B12/folate deficiency
- HIV or other viral infection
- Copper deficiency
- Alcohol abuse
- Medications (esp. methotrexate, azathioprine, recent chemotherapy)
- Autoimmune conditions (ITP, Felty syndrome, SLE etc.)
- Congenital syndromes (Fanconi anemia etc.)
- Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)
65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

- Normal Range
- B12 level - Normal
- Folate - Normal
- Thyroid - Normal
- No toxic medications
- No alcohol use
- No chronic illness
Bone Marrow Biopsy

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From: NCCN Guidelines for Patients: MDS
The Bone Marrow
Bone Marrow Dysplasia
Chromosomes and Mutation Testing

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Bone Marrow Biopsy

65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

Too many cells in the bone marrow
Developing cells are dysplastic (abnormal)
No extra ‘blasts’ seen
Chromosomes are NORMAL
Classification of MDS Subtypes
<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Blood findings</th>
<th>Bone Marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with unilineage dysplasia</td>
<td>RCUD</td>
<td>• Unicytopenia; occasionally bicytopenia</td>
<td>• Unilineage dysplasia (≥10% of cells in one myeloid lineage)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No or rare blasts (&lt;1%)</td>
<td>• &lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• &lt;15% of erythroid precursors are ring sideroblasts</td>
</tr>
<tr>
<td>Refractory anemia (RA)</td>
<td>RARS</td>
<td>• Anemia</td>
<td>• ≥15% of erythroid precursors are ring sideroblasts</td>
</tr>
<tr>
<td>Refractory neutropenia (RN)</td>
<td></td>
<td>• No or rare blasts (&lt;1%)</td>
<td>• Erythroid dysplasia only</td>
</tr>
<tr>
<td>Refractory thrombocytopenia (RT)</td>
<td></td>
<td></td>
<td>• &lt;5% blasts</td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td>Del(5q)</td>
<td>• Anemia</td>
<td>• Isolated 5q31 deletion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Usually normal or increased platelet count</td>
<td>• Normal to increased megakaryocytes with hypolobated nuclei</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No or rare blasts (&lt;1%)</td>
<td>• &lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No Auer rods</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>RCMD</td>
<td>• Cytopenia(s)</td>
<td>• ≥10% of cells in ≥2 myeloid lineages dysplastic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No or rare blasts (&lt;1%)</td>
<td>• &lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No Auer rods</td>
<td>• No Auer rods</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &lt;1 x 10⁹/L monocytes</td>
<td>• ±15% ring sideroblasts</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 1</td>
<td>RAEB-1</td>
<td>• Cytopenia(s)</td>
<td>• Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &lt;5% blasts</td>
<td>• 5-9% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No Auer rods</td>
<td>• No Auer rods</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &lt;1 x 10⁹/L monocytes</td>
<td></td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 2</td>
<td>RAEB-2</td>
<td>• Cytopenia(s)</td>
<td>• Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 5-19% blasts</td>
<td>• 10-19% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ±Auer rods</td>
<td>• ±Auer rods</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &lt;1 x 10⁹/L monocytes</td>
<td></td>
</tr>
<tr>
<td>MDS - unclassified</td>
<td>MDS-U</td>
<td>• Cytopenia(s)</td>
<td>• Minimal dysplasia but clonal cytogenetic abnormality considered presumptive evidence of MDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≤1% blasts</td>
<td>• &lt;5% blasts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Blood findings</th>
<th>Bone Marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia with ring sideroblasts and thrombocytosis</td>
<td>RARS-T</td>
<td>• Anemia • No blasts • ≥450 x 10^9/L platelets</td>
<td>• ≥15% of erythroid precursors are ring sideroblasts • Erythroid dysplasia only • &lt;5% blasts • proliferation of large megakaryocytes</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia, type 1</td>
<td>CMML-1</td>
<td>• &gt;1 x 10^9/L monocytes • &lt;5% blasts</td>
<td>• Unilineage or multilineage dysplasia • &lt;10% blasts</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia, type 2</td>
<td>CMML-2</td>
<td>• &gt;1 x 10^9/L monocytes • 5%-19% blasts or Auer rods</td>
<td>• Unilineage or multilineage dysplasia • 10%-19% blasts or Auer rods</td>
</tr>
<tr>
<td>Atypical chronic myeloid leukemia</td>
<td>aCML</td>
<td>• WBC &gt; 13 x 10^9/L • Neutrophil precursors &gt;10% • &lt;20% blasts</td>
<td>• Hypercellular • &lt;20% blasts • BCR-ABL1 negative</td>
</tr>
<tr>
<td>Juvenile myelomonocytic leukemia</td>
<td>JMML</td>
<td>• &gt;1 x 10^9/L monocytes • &lt;20% blasts</td>
<td>• Unilineage or multilineage dysplasia • &lt;20% blasts • BCR-ABL1 negative</td>
</tr>
<tr>
<td>MDS/MPN – unclassified (‘Overlap Syndrome’)</td>
<td>MDS/MPN-U</td>
<td>• Dysplasia with myeloproliferative features • No prior MDS or MPN</td>
<td>• Dysplasia with myeloproliferative features</td>
</tr>
</tbody>
</table>

## World Health Organization MDS categories (2016)

<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)³</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), &lt;1 x 10⁹/L monocytes</td>
<td>Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, ± 15% ring sideroblasts, &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with excess blasts-1 (MDS-EB-1)</td>
<td>Cytopenia(s), ≤2%–4% blasts, &lt;1 x 10⁹/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, &lt;1 x 10⁹/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</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>
<tr>
<td>MDS with excess blasts in transformation (MDS-EB-T)²</td>
<td>Cytopenias, 5%–19% blasts</td>
<td>Multilineage dysplasia, 20%–29% blasts, ± Auer rods</td>
</tr>
</tbody>
</table>
Prognosis & Risk Assessment
65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

**Diagnosis:**
MDS with single lineage dysplasia - **MDS-SLD**
International Prognostic Scoring System

<table>
<thead>
<tr>
<th>Cytogenetic Risk Group</th>
<th>IPSS Karyotype Abnormalities (7 categories)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Normal, -Y, del(5q), del(20q)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, any other single or double abnormality</td>
</tr>
<tr>
<td>Poor</td>
<td>Complex with ≥ 3 abnormalities, anomaly of chromosome 7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IPSS Parameter</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic Risk Group</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Bone Marrow Blast %</td>
<td>≤ 5%</td>
<td>5%-10%</td>
<td>11%-20%</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Number of Cytopenias</td>
<td>0 or 1</td>
<td>2 or 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

Definition of Cytopenias
- Hemoglobin < 10 g/dL
- Neutrophil Count < 1.80 x 10^9/L
- Platelet Count < 100 x 10^9/L

<table>
<thead>
<tr>
<th>IPSS Risk Group</th>
<th>Points</th>
<th>% of Patients</th>
<th>Median survival, years</th>
<th>Time to 25% with AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>33%</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5 - 1</td>
<td>38%</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5 - 2</td>
<td>22%</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>High</td>
<td>≥ 2.5</td>
<td>7%</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

International Prognostic Scoring System

LOWER Risk
- Low
- Int-1

HIGHER Risk
- Int-2
- High

Overall Survival, Years

Time to AML Evolution, Years

Patients, %
# IPSS-Revised (IPSS-R)

<table>
<thead>
<tr>
<th>Cytogenetic Risk Group</th>
<th>IPSS-R Karyotype Abnormalities (19 categories)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>del(11q), -Y</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones</td>
</tr>
<tr>
<td>Poor</td>
<td>der(3q), -7, double with del(7q), complex with 3 abnormalities</td>
</tr>
<tr>
<td>Very Poor</td>
<td>Complex with &gt; 3 abnormalities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IPSS-R Parameter</th>
<th>Categories and Associated Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic Risk Group</td>
<td>Very good</td>
</tr>
<tr>
<td>Bone Marrow Blast %</td>
<td>≤ 2%</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>≥ 10</td>
</tr>
<tr>
<td>Platelet Count (x 10⁹/L)</td>
<td>≥ 100</td>
</tr>
<tr>
<td>Absolute Neutrophil Count (x 10⁹/L)</td>
<td>≥ 0.8</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IPSS-R Risk Group</th>
<th>Points</th>
<th>% of Patients</th>
<th>Median survival, years</th>
<th>Time to 25% with AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>≤ 1.5</td>
<td>19%</td>
<td>8.8</td>
<td>Not reached</td>
</tr>
<tr>
<td>Low</td>
<td>&gt; 1.5 - 3</td>
<td>38%</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt; 3 - 4.5</td>
<td>20%</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 4.5 - 6</td>
<td>13%</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt; 6</td>
<td>10%</td>
<td>0.8</td>
<td>0.73</td>
</tr>
</tbody>
</table>

### Limitations of the IPSS-R

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Included karyotypes (19 categories)</th>
<th>Median survival, months</th>
<th>Proportion of patients in this group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>del(11q), -Y</td>
<td>60.8</td>
<td>2.9%</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)</td>
<td>48.6</td>
<td>65.7%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones</td>
<td>26.1</td>
<td>19.2%</td>
</tr>
<tr>
<td>Poor</td>
<td>der(3q), -7, double with del(7q), complex with 3 abnormalities</td>
<td>15.8</td>
<td>5.4%</td>
</tr>
<tr>
<td>Very poor</td>
<td>Complex with &gt; 3 abnormalities</td>
<td>5.9</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

### Parameter and Categories and Associated Scores

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cytogenetic risk group</th>
<th>Categories</th>
<th>Associated Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival, years</td>
<td></td>
<td>Very good</td>
<td>Good</td>
</tr>
<tr>
<td>-</td>
<td>≤ 2%</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Marrow blast proportion</td>
<td>&gt; 2% - &lt; 5%</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>≥ 10</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count (x 10^9/L)</td>
<td>≥ 100</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Abs. neutrophil count (x 10^9/L)</td>
<td>≥ 0.8</td>
<td>0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Risk group and Points

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Points</th>
<th>% of Patients</th>
<th>Median survival, years</th>
<th>Time until 25% of patients develop AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>≤ 1.5</td>
<td>19 %</td>
<td>8.8</td>
<td>Not reached</td>
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<tr>
<td>Low</td>
<td>&gt; 1.5 – 3</td>
<td>38 %</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt; 3 – 4.5</td>
<td>20 %</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 4.5 – 6</td>
<td>13 %</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt; 6</td>
<td>10 %</td>
<td>0.8</td>
<td>0.73</td>
</tr>
</tbody>
</table>

- Considers only UNTREATED patients
- IPSS-R does not consider somatic mutations
- Somatic mutations are common in MDS
- Several mutated genes have prognostic significance independent of the IPSS-R
65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

**Diagnosis:**
MDS with single lineage dysplasia - **MDS-SLD**
WPSS - Very Low Risk
IPSS - Low Risk
IPSS-R - Very Low Risk

**Mutations?**
Gene Mutations in MDS

Tyrosine Kinase Pathway
- JAK2
- KRAS
- BRAF
- NRAS
- RTK's
- PTPN11
- CBL

Transcription Factors
- RUNX1
- ETV6
- GATA2
- WT1
- PHF6

Others
- TP53
- NPM1
- NOTCH?
- MAML?
- ZSWIM4?
- UMODL1?

Epigenetic Dysregulation
- IDH 1 & 2
- DNMT3A
- EZH2
- TET2
- UTX
- ASXL1
- ATRX
- SETBP1

Splicing Factors
- SF3B1
- U2AF1
- SRSF2
- SF1
- SF3A1
- U2AF2
- PRPF40B
- PRPF8
30% of MDS patients have a mutation in one of these genes

These mutations indicate more severe disease!


Impact of Mutations by IPSS Group

**TP53**

**ETV6**

**ASXL1**

**EZH2**

**RUNX1**

Impact of Mutations by IPSS-R Group

TP53
ETV6
ASXL1
EZH2
RUNX1

Very Low
Low
Intermediate
Prognostic Mutations by Blast % (<5%)

-\log_{10}(p-value)

Hazard Ratio after adjustment for IPSS-R Risk Group

$\geq 4.0$

35%

$p = 0.05$
Prognostic Mutations by Blast % (5-30%)
Clinical Sequencing and Banking

Targeted Massively Parallel Sequencing

<table>
<thead>
<tr>
<th>Epigenetic Regulator</th>
<th>Splicing Factor</th>
<th>Transcription Factor</th>
<th>Kinase Signalling</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASXL1</td>
<td>LUC7L2</td>
<td>CEBPA</td>
<td>BRAF</td>
<td>CDH11</td>
</tr>
<tr>
<td>ATRX</td>
<td>PRPF40B</td>
<td>ETV6</td>
<td>CBL</td>
<td>CUL1</td>
</tr>
<tr>
<td>BAP1</td>
<td>PRPF8</td>
<td>GATA2</td>
<td>CBLB</td>
<td>CUX1</td>
</tr>
<tr>
<td>BCOR</td>
<td>SF1</td>
<td>MLL</td>
<td>FLT3</td>
<td>FMN2</td>
</tr>
<tr>
<td>BCORL1</td>
<td>SF3A1</td>
<td>PHF6</td>
<td>JAK2</td>
<td>GNAS</td>
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<td>DNMT3A</td>
<td>SF3B1</td>
<td>RUNX1</td>
<td>KIT</td>
<td>MYBL2</td>
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<td>EED</td>
<td>SRSF2</td>
<td>TP53</td>
<td>KRAS</td>
<td>NPM1</td>
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<td>EZH2</td>
<td>U2AF1</td>
<td>WT1</td>
<td>MPL</td>
<td>RAD21</td>
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<td>IDH1</td>
<td>U2AF2</td>
<td>NRAS</td>
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<td>IDH2</td>
<td>ZRSR2</td>
<td>PTEN</td>
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<td>JARID2</td>
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<td>SETBP1</td>
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<td>SUZ12</td>
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<tr>
<td>TET2</td>
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</tr>
</tbody>
</table>

Clinical Information

Viable Cells
Tumor DNA/RNA
Germline DNA

Biorepository

Extensive Genotypic Annotation
Risk Adapted Patient Specific Therapy
Treatment Options for MDS

- Observation
- Erythropoiesis stimulating agents
- Granulocyte colony stimulating factor
- Iron chelation
- Red blood cell transfusion
- Platelet transfusion
- Lenalidomide
- Immune Suppression
- Hypomethylating agent
- Stem cell transplantation

Clinical Trials – always the best option
MDS Treatment is Highly Risk Stratified

Myelodysplastic Syndromes

**Lower Risk**
- Observation
- EPO
- Lenalidomide
- Immune suppression
- Iron Chelation

**Higher Risk**
- Azacitidine
- Decitabine
- Allo-HSCT
- Clinical Trials
Primary Goal: to improve QUALITY OF LIFE

1. Do I need to treat at all?
   - No advantage to early aggressive treatment
   - Observation is often the best approach

2. Are transfusions treatment?
   - No! They are a sign that treatment is needed.
Guidelines for Lower Risk MDS

Primary Goal: to improve QUALITY OF LIFE

NCCN Guidelines® Version 2.2013
Myelodysplastic Syndromes

IPSS: Low/Intermediate-1
WPSS: Very Low, Low, Intermediate

Clinically significant cytopenia(s)
Supportive care as an adjunct to treatment

Symptomatic anemia
No del(5q) ± other cytogenetic abnormalities
Clinically relevant thrombocytopenia or neutropenia

del(5q) ± other cytogenetic abnormalities
Treating Lower Risk MDS

**Primary Goal**: to improve QUALITY OF LIFE

What if treatment is needed?

1. Is my most effective therapy likely to work?
   - Lenalidomide (Revlimid)

In del(5q) – response rates are high

50%-70% respond to treatment

Median 2-years transfusion free!
Treating Lower Risk MDS

Primary Goal: to improve QUALITY OF LIFE

Is my second most effective therapy likely to work?

- Red blood cell growth factors
- Erythropoiesis Stimulating Agents (ESAs)
- Darbepoetin alfa (Aranesp)
- Epoetin alfa (Procrit, Epogen)
- Lance Armstrong Juice → EPO
Primary Goal: to improve **QUALITY OF LIFE**

ESAs – act like our own erythropoietin

<table>
<thead>
<tr>
<th>Serum EPO level (U/L)</th>
<th>RBC transfusion requirement</th>
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</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>+2 pts</td>
</tr>
<tr>
<td>100-500</td>
<td>+1 pt</td>
</tr>
<tr>
<td>&gt;500</td>
<td>-3 pts</td>
</tr>
<tr>
<td></td>
<td>&lt;2 Units / month = +2 pts</td>
</tr>
<tr>
<td></td>
<td>≥2 Units / month = -2 pts</td>
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</tbody>
</table>

Total Score

<table>
<thead>
<tr>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High likelihood of response: &gt; +1</td>
</tr>
<tr>
<td>Intermediate likelihood: -1 to +1</td>
</tr>
<tr>
<td>Low likelihood of response: &lt; -1</td>
</tr>
</tbody>
</table>

Hellstrom-Lindberg E et al *Br J Haem* 2003; 120:1037
Treating Lower Risk MDS

Primary Goal: to improve QUALITY OF LIFE

Is a combination of LEN +/- ESA likely to work?

In non-del(5q) MDS patients:

<table>
<thead>
<tr>
<th></th>
<th>LEN (n = 160)</th>
<th>Placebo (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>99 patients after 4 cycles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC-TI ≥ 8 Weeks</td>
<td>26.9</td>
<td>2.5</td>
</tr>
<tr>
<td>RBC-TI ≥ 24 Weeks</td>
<td>17.5</td>
<td></td>
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</table>

131 included

<table>
<thead>
<tr>
<th></th>
<th>LEN + EPO n = 50</th>
<th>LEN n = 49</th>
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<tbody>
<tr>
<td>≤ 100 mU/mL (n = 40)</td>
<td>52%</td>
<td>30.6%</td>
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<tr>
<td>100–200 mU/mL (n = 27)</td>
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<tr>
<td>200–500 mU/mL (n = 30)</td>
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<tr>
<td>&gt; 500 mU/mL (n = 58)</td>
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<td></td>
</tr>
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</table>

HI – E (IWG 2006)

RBC - TI

32% 18.4%  P = 0.12


Toma et al, Leukemia. 2016 Apr;30(4):897-905
Treating Lower Risk MDS

Primary Goal: to improve QUALITY OF LIFE

What my next most effective therapy?

- Immunosuppression

Some MDS patients have features of aplastic anemia

- Hypoplastic bone marrow (too few cells)
- PNH clones
- Certain immune receptor types (HLA-DR15)
Immune Suppression for MDS

Primary Goal: to improve QUALITY OF LIFE

Swiss/German Phase III RCT of ATG + Cyclosporin (88 patients)

Mostly men with Lower Risk MDS

CR+PR: 29% vs. 9%

No effect on survival

Predictors of Response:
- hypocellular aspirate
- lower aspirate blast %
- younger age
- more recent diagnosis

Iron Balance and Transfusions

- Daily intake: 1.5 mg (0.04%)
  - Tightly regulated

- Daily losses only: 1.5 mg (0.04%)
  - Not regulated!

- 3-4 grams of Iron in the body

- Every three units of blood
What About Iron Chelation?

More transfusions and elevated ferritin levels are associated with poor outcomes in MDS patients.

Are these drivers of prognosis or just reflective of disease?

Retrospective studies suggest survival advantage!

small prospective and large population based Medicare studies show survival benefit, INCLUDING hematologic responses (11-19%).

I consider treatment in lower risk, transfusion dependent patients with long life expectancy after 20+ transfusions.

How to Chelate Iron

Three ways are FDA approved:

- Deferoxamine (Desferal) – subcutaneous pump 8-12 hrs/day
- Deferasirox (Exjade/Jadenu) – powder/pill – once per day
- Deferiprone (Ferriprox) – oral pill form – 3x per day

But side effects and adverse events can be significant!

- Deferasirox – renal, hepatic failure and GI bleeding
- Deferiprone – agranulocytosis (no neutrophils!)
Guidelines for Lower Risk MDS

Primary Goal: to improve QUALITY OF LIFE

1. Do I need to treat? - symptomatic cytopenias
2. Is LEN likely to work? - del(5q) or after ESA
3. Are ESA likely to work? - Serum EPO < 500
4. Is IST likely to work? - hypocellular, DR15, PNH
5. Think about iron! - 20 or more transfusions
6. Consider AZA/DEC
7. Consider HSCT or clinical trial!
Novel Treatments for Lower Risk MDS
Oral Azacitidine – in Phase III clinical trials

- more convenient
- similar response rates
- more GI side effects

May be more effective as it can be taken longer
Low Dose Azacitidine/Decitabine

Decitabine 20 mg/m² intravenously daily for 3 days - 60% dose - 70% ORR
Azacitidine 75 mg/m² intravenously daily for 3 days - 43% dose - 49% ORR

Jabbour et al., Blood 2017 130:1514-1522.
Platelet Growth Factors

**Eltrombopag or Romiplostim** - TPO mimetics

Eltrombopag and Romiplostim - approved, but not in MDS

Initial concern about increasing blasts and risk of AML

Follow-up suggests Romiplostim safe in lower risk patients

Mittleman M et al *ASH Abstracts*, 2013. Abstract #3822
Kantarjian H et al *ASH Abstracts*, 2013. Abstract #421
Luspatercept

ESAs
TPO mimetics
G-CSF (neupogen)

EPO/ESAs

Hemoglobin synthesis

BFU-E → CFU-E → Pro E → Baso E → Poly E → Ortho E → Retic → RBC

TGF-β
Luspatercept

ESAs
TPO mimetics
G-CSF (neupogen)

EPO/ESAs

Hemoglobin synthesis

BFU-E  CFU-E  Pro E  Baso E  Poly E  Ortho E  Retic  RBC

TGFβ
Promoting Red Cell Production

Luspatercept (ACE-536) and Sotatercept (ACE-011)
Promoting Red Cell Production

Luspatercept (ACE-536) and Sotatercept (ACE-011)
Increase in Mean Hemoglobin in LTB Patients with > 3 Months of Treatment (Extension Study)

- 11/13 (85%) HI-E responders; median time to response: 6 weeks

LTB: Low transfusion burden patients (< 4 Units/8 wk, Hb <10 g/dL)
Guidelines for Lower Risk MDS

Special Considerations:

**Transfusion Dependence**
- Indication for treatment – even with AZA/DEC, consider chelation

**Del(5q)**
- High response rate to LEN even if other abnormalities

**Serum EPO level**
- Used to predict EPO response, > 500 → unlikely to work

**Indication for G-CSF**
- used to boost EPO, not for primary neutropenia

**Immunosuppresive Therapy**
- ≤ 60y, hypocellular marrow, HLA-DR15+, PNH clone
To all of our AMAZING PATIENTS and our INFUSION CENTER nurses and staff!
High Risk MDS and Novel Therapies: What’s on the Horizon?

Rafael Bejar MD, PhD

MDS Foundation

Patients & Caregivers LIVING with MDS Forums

February 3, 2018
Overview

• Treatment of Higher Risk MDS

• Stem Cell Transplantation

• Novel Drug Therapies

• Immune Therapies
Low Blood Counts

71 year-old man with big red cells and low blood counts that developed over the past 6 months.
Low Blood Counts

71 year-old man with big red cells and low blood counts that developed over the past 6 months.

Way too many cells in the bone marrow
4% blasts in aspirate

Dysplasia in all three cell types

Normal Karyotype (chromosomes ok)
Treatment of Higher Risk MDS
Guidelines for Higher Risk MDS

Goal: to improve DURATION OF LIFE

IPSS: INT-2, HIGH
WPSS: HIGH, VERY HIGH

High-intensity therapy candidate

Transplant candidate and Donor available

Yes → Allo (HSCT) → If relapse → AZA/DEC or Clinical trial

No → AZA (preferred) (category 1)/DEC or High-intensity chemotherapy or Clinical trial

Not high-intensity therapy candidate

AZA (preferred) (category 1)/DEC or Clinical trial

Continue

Response

No response or relapse

Clinical trial or Supportive care
Inhibitors of DNA methyl transferases:

Both incorporate into DNA and cause hypomethylation (DEC > AZA)

AZA preferentially causes DNA damage and induces apoptosis
AZA-001 Phase III: AZA vs. Id-ARA-C vs. supportive care

OS benefit: + 9.5 mos

Time to AML: 17.8 vs. 11.5 mos

TI: 45% vs. 11%

Azacitidine Response:

ORR: ~50%

CR: ~17%

Median time to response: 3 cycles (81% by cycle 6)
Decitabine Phase III Trial
Dosed q8h x 3 days per 28 days
CR: 17%
CR+PR: 30%

ADOPT Trial and 3-Schedule Trial
Dosed q24h x 5 days per 28 days
CR: 17%
CR+PR: 32%

ORR: 52% (+ heme response)
Best response: 50% at 2 cycles

Major Toxicity:
- Neutropenia: 31% (FN 11%)
- Thrombocytopenia: 18%
Azacitidine and Decitabine are imperfect drugs:
- Treatment is intensive – 5 to 7 days every 4 weeks
- Overall response rate is only 45% and CR rate is ~15%.
- Responses can take 4-6 months to appear!
- Counts get worse for EVERYONE initially – expected
  - Risks include neutropenic fever, bleeding, new transfusion requirements

But, they’re not all bad:
- HMAs are generally well tolerated
  - No hair loss or mucositis
  - Little to no nausea or vomiting
  - Common side effects are fatigue and constipation (Zofran ?)
Guidelines for Higher Risk MDS

Goal: to improve **DURATION OF LIFE**

**Special Considerations:**

Refer for Transplant Early
- Even patients in their 70’s can benefit from RIC transplant

AZA > DEC (for now)
- AZA has been shown to have a survival advantage, DEC has not (yet)

Don’t forget **Quality of Life**
- Consider treatment palliative and weigh against patient needs

Look for Clinical Trials
- Few option after AZA are available and none are approved
Outcomes After Azacitidine

**Reasons for “failure” in azacitidine failure study**

- **9% didn’t tolerate AZA** (69% were not responding, 31% had an initial response)
- **55% primary failure** (progression in 60%, stable disease without response in 40%)
- **36% secondary failure** after initial response (best response: CR 20%, PR 7%, HI 73%)

**Outcomes after failure**

- Median overall survival for whole cohort post-AZA: **5.6 months**
- 2 year survival: **15%**
- Favorable factors: female, younger (<60), better risk karyotype, <10% blasts, some response to azacitidine

Comparison to decitabine failures @ MDACC: **median survival 4.3 months, n=87**

Outcomes After Azacitidine

- Data available on 435 pts
  - from AZA001, J9950, J0443, French compassionate program
- Overall median survival after azacitidine failure: 5.6 months

<table>
<thead>
<tr>
<th>Subsequent therapy</th>
<th>Number of patients (%)</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic transplant</td>
<td>37 (9%)</td>
<td>19.5 months</td>
</tr>
<tr>
<td>Investigational therapy (e.g. IMiD, HDACi, other)</td>
<td>44 (10%)</td>
<td>13.2 months</td>
</tr>
<tr>
<td>Intensive cytotoxic therapy (e.g., 3&amp;7)</td>
<td>35 (8%)</td>
<td>8.9 months</td>
</tr>
<tr>
<td>Low-dose chemotherapy (e.g. LDAC, 6-MP)</td>
<td>32 (7%)</td>
<td>7.3 months</td>
</tr>
<tr>
<td>Palliative / supportive care</td>
<td>122 (28%)</td>
<td>4.1 months</td>
</tr>
<tr>
<td>Subsequent therapy unknown</td>
<td>165 (38%)</td>
<td>3.6 months</td>
</tr>
</tbody>
</table>
We need **BETTER** therapies!

We need **MORE** therapies!
Stem Cell Transplantation
Stem Cell Transplantation

The Allogeneic Transplant Process

1. **Collection**
   - Stem cells are collected from the patient's bone marrow or blood.

2. **Processing**
   - Bone marrow or peripheral blood is taken to the processing laboratory where the stem cells are concentrated and prepared for the freezing process.

3. **Cryopreservation**
   - Bone marrow or blood is preserved by freezing (cryopreservation) to keep stem cells alive until they are infused into the patient's bloodstream.

4. **Chemotherapy**
   - High dose chemotherapy and/or radiation therapy is given to the patient.

5. **Infusion**
   - Thawed stem cells are infused into the patient.

**Donor**

**Patient**
Goal of Hematopoietic Stem Cell Transplantation:

#1) Replace a dysfunction host hematopoietic system with normal, healthy donor marrow.

#2) Allow the donor immune system to destroy the abnormal, diseased host cells (MDS).
<5% of patients with MDS currently undergo allogeneic SCT

“Only curative therapy”

Patients who go in to RIC allo SCT with <10% blasts appear to have lower relapse

Optimal timing, pre-transplant therapy, conditioning unclear; usually reserved for IPSS Int-2/High (IBMTR Markov analysis)

Transplant candidate
Donor identified

Survives transplant; MDS cured! (35-40%)

Survives transplant; MDS recurs/persists (30-40%)

Dies from complication of transplant (20-25%)


Slide borrowed from Dr. David Steensma
Obstacles to Transplantation

Graft Rejection
- need to suppress the host immune system

Toxicity
- infection
- organ damage
- graft versus host disease

Finding a Donor
- siblings match only 25% of the time
- and are often too old or ill to donate
Overcoming Obstacles

Avoiding Graft Rejection
– better approaches to immune suppression

Less Toxicity
– better supportive care
– better antigen matching
– reduced intensity conditioning

Alternative Sources for Stem Cells
– haploidentical – “half” match
– umbilical cord blood stem cells
Reduce intensity conditioning transplantation in Older Patients with De Novo MDS

Trends in Allogeneic Transplants by Transplant Type and Recipient Age*
1990-2010

* Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma
Allogeneic Transplants for Age > 20yrs, Registered with the CIBMTR, 1993-2010
- by Donor Type and Graft Source -
**TP53 mutated MDS**

*Poor prognosis due to early relapse*

**Survival**

- *TP53 mutation*
  - Median OS = 8 months
- *No TP53 mutation*

**Relapse**

- *TP53 mutation*
- *No TP53 mutation*

\[ p < 0.0001 \]
Novel Treatments for Higher Risk MDS
Guidelines for Higher Risk MDS

**Goal:** to improve **DURATION OF LIFE**

**Special Considerations:**

- **Refer for Transplant Early**
  - Even patients in their 70’s can benefit from RIC transplant

- **AZA > DEC (for now)**
  - AZA has been shown to have a survival advantage, DEC has not (yet)

- **Don’t forget Quality of Life**
  - Consider treatment palliative and weigh against patient needs

- **Look for Clinical Trials**
  - Few option after AZA are available and none are approved
### Rigosertib Phase III Result

<table>
<thead>
<tr>
<th></th>
<th>Rigosertib N = 199</th>
<th>BSC N = 100</th>
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</thead>
<tbody>
<tr>
<td><strong>Number (%) of deaths</strong></td>
<td>161 (81%)</td>
<td>81 (81%)</td>
</tr>
<tr>
<td><strong>Median follow-up (months)</strong></td>
<td>17.6</td>
<td>19.5</td>
</tr>
<tr>
<td><strong>Median survival (months)</strong></td>
<td><strong>8.2</strong></td>
<td>5.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>6.0 - 10.1</td>
<td>4.1 - 9.3</td>
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<tr>
<td><strong>Stratified HR (rigosertib/BSC)</strong></td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.67 - 1.14</td>
<td></td>
</tr>
<tr>
<td><strong>Stratified log-rank p-value</strong></td>
<td>0.33</td>
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</tbody>
</table>

#### Overall Survival

- **Medians:**
  - RIG: 8.2 mo
  - BSC: 5.9 mo
  - Stratified log-rank P = 0.33
  - HR = 0.87 (95% CI: 0.67-1.14)

- **At risk:**
  - RIG: 199, 157, 114, 86, 52, 29, 11, 7, 4, 3, 1
  - BSC: 100, 71, 47, 35, 19, 14, 8, 3, 2, 1
ONTIME Trial: Median Overall Survival for Pts with Primary HMA Failure - Blinded, Centralized Assessment

Per Prebet 2011, “Primary HMA Failure” was defined as either no response to or progression during HMA therapy

ASH 2014
SGI-110 Phase II Results

<table>
<thead>
<tr>
<th></th>
<th>60 mg/m² (n=53)</th>
<th>90 mg/m² (n=49)</th>
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<tbody>
<tr>
<td>8-week <strong>RBCs Transfusion</strong> Independent n (%)</td>
<td>7/27 (26%)</td>
<td>5/24 (21%)</td>
</tr>
<tr>
<td>8-week <strong>Platelet Transfusion</strong> Independent n (%)</td>
<td>4/13 (31%)</td>
<td>5/15 (33%)</td>
</tr>
</tbody>
</table>

Decitabine + Guanosine = SGI-110
Oral Decitabine + CDAi

Pharmacokinetics

Decitabine PK profile, IV vs oral, without/with CDAi

- Oral DAC alone 20 mg
- Oral DAC alone 30 mg
- Oral DAC alone 40 mg
- IV DAC 20mg/m^2
- 40:20 mg ASTX727 (1)
- 60:20 mg ASTX727 (2)
- 100:20 mg ASTX727 (3)
- 100:40 mg ASTX727 (4)
- 100:30 mg ASTX727 (5)

Time, hr

0 2 4 6 8
Pevonedistat

Has activity in AML when combined with azacitidine

Now in a phase III clinical trial in MDS/CMML/sAML
Other Epigenetic Drugs

HDAC inhibitor

HDAC

BET inhibitor

BET

DOT1L inhibitor

DOT1L

DNMT inhibitor

DNMT3A

LSD1 inhibitor

LSD1

IDH inhibitors

IDH1/2 mutant

TET2

deacetylated histone tail

histone

methylated cytosine

acetylated histone tail

methylated histone tail

demethylated cytosine
Immune Regulation

PD1 and PD-L1 Inhibitors

Phase I/II Trial will be opening here at UCSD
Immunologic Therapy

Killer T-cell

Tumor Cell

Plasma B-cell

Chimeric Antigen Receptor

Monoclonal antibody

Immune receptor

CD3ζ

FcεRIγ

VH

VL

Cγ1

Cγ2

Cγ3

scFv

Hinge

TM

Signaling chain
Immuneologic Therapy

Chimeric Antigen Receptor Modified T-cell

Tumor Cell
From Genetic Biomarkers to Disease Targets

Skin Biopsy

Bone Marrow Aspirate

Blood Apheresis

Isolation of Autologous Killer T-Cells and Antigen Presenting B-Cells

Whole Exome and Whole Transcriptome Sequencing

CD34+ and monocytes

Somatic Mutations Expressed by MDS Cells
Genetically Targeted Immunotherapy

**Isolation of Autologous Killer T-Cells**
- Incubation of Antigen Presenting Cells And Killer T-Cells
- *Ex-vivo* Selection and Expansion of Antigen Reactive T-Cells

**Somatic Mutations Expressed by MDS Cells**
- Antigen Presenting Cells + Synthetic HLA-Compatible Mutated Peptide Fragments

**Patient Infusion!**
### MDS Center of Excellence at UC San Diego

<table>
<thead>
<tr>
<th>Name</th>
<th>Name</th>
<th>Department</th>
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<tbody>
<tr>
<td>Marla McArdle</td>
<td>Soo Park</td>
<td>Bejar Clinic</td>
</tr>
<tr>
<td>Jennifer Galvan</td>
<td>Olivia Reynolds</td>
<td></td>
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<tr>
<td>Elizabeth BroomeHuanyou Wang</td>
<td>- Hematopathology</td>
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<tr>
<td>Edward Ball</td>
<td>Peter Curtin</td>
<td>BMT Group</td>
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<tr>
<td>Matthew Wieduwilt</td>
<td>Divya Koura</td>
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<tr>
<td>Carolyn Mulroney</td>
<td>Caitlin Costello</td>
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<tr>
<td>Januario Castro</td>
<td>Dimitrios Tzachanis</td>
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<td>Aaron Goodman</td>
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<td>Sandy Shattil</td>
<td>John Adamson</td>
<td>Hematology Group</td>
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<tr>
<td>Catriona Jamieson</td>
<td>Michael Choi</td>
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<td>Erin Reid</td>
<td>Tom Kipps</td>
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<tr>
<td>Natalie Galanina</td>
<td>Annette Von Drygalski</td>
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<tr>
<td>Lynn Bemiller</td>
<td>Tiffany Tanaka</td>
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### Bejar Lab

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Tim Luger</td>
<td>Soo Park</td>
</tr>
<tr>
<td>Tiffany Tanaka</td>
<td>Brian Reilly</td>
</tr>
<tr>
<td>Emily Wheeler</td>
<td>Armon Azizi</td>
</tr>
<tr>
<td>Robyn Raban</td>
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</tbody>
</table>

To all of our AMAZING PATIENTS and our INFUSION CENTER nurses and staff!