The Myelodysplastic Syndromes

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Myelodysplastic Syndromes

- A group of malignant hematopoietic disorders characterized by:
  - Bone marrow failure with resultant cytopenia and related complications
  - Dysplastic morphology
  - Tendency to progress to AML
- Overall incidence 3-4/100,000
  - ≈ 10,000/yr in US


MDS: Etiology

**Acquired:**
- De novo: Cause is unknown
  - Secondary:
    - Toxic exposure:
      - Therapeutic: alkylating agents, Topo-II inhibitors, ∝-emitters (32P), auto RCT
      - Environmental/occupational (benzene), Tobacco
    - Antecedent hematological disorders:
      - Aplastic anemia
      - PNH

**Heritable:**
- Constitutional genetic disorders
  - Trisomy 8 mosaicism
  - Familial monosomy 7
- Neurofibromatosis 1
- Embryonal dysgenesis (del12p)
- Congenital Neutropenia
  - Kostmann, Schwartzman-Diamond
  - DNA repair deficiencies
  - Fanconi anemia, AT, Bloom syndrome
  - Pharmacogenomic polymorphisms (GSTq1-null)

Epidemiology

- Overall incidence: 4.4 per 100,000

MDS presents a diagnostic challenge

- MDS requires a morphologic diagnosis
  - minimum criterion is dysplasia in ≥ 10% of any myeloid lineages (also seen in AML, CMML, MPN)
- Assessment of cellular atypia is an inexact art
  - interobserver variability
  - specimen handling and processing
- Features of dysmyelopoiesis overlap with metabolic and non-malignant hematologic disorders
- MDS requires a diagnosis of exclusion

Clinical Entities overlap with MDS

AA, aplastic anemia; LGL, large-granular lymphocyte leukemia; MPN, myeloproliferative neoplasms; PNH, paroxysmal nocturnal hemoglobinuria; PRCA, pure red cell aplasia

**MDS: Clinical Presentation**

- Patients typically present with symptoms related to bone marrow failure, such as fatigue, infections and/or bleeding
- Anemia is the most common cytopenia in MDS
  - Solitary cytopenia in 30%
  - Usually hypoproliferative: low reticulocyte count
- Neutropenia in > 50% of patients
  - 30-35% have ANC <1000-1500/μl
  - Only 10% have infection as presenting or recurring problem
  - No indication for routine antibacterial prophylaxis
  - Patient education for neutropenic fever precautions essential
- Thrombocytopenia complicates 25-50% of patients
  - Rarely only lineage affected
  - PLT dysfunction has been described causing prolonged bleeding time and abnormal platelet aggregation studies

**MDS: Clinical Presentation**

- Thrombocytosis can be seen with certain subtypes of MDS such as Del 5q syndrome, and RARS-T
- Lymphadenopathy is uncommon.
- Splenomegaly is also uncommon in MDS, but may be seen in MDS/MPN overlap syndromes such as CMML

**Cytopenia: Basic Diagnostic Evaluation**

- Peripheral blood counts, CMP, reticulocyte count
- Review of the peripheral blood smear
- Laboratory tests:
  - Iron studies, ferritin, B12, folate levels, EPO level
  - SPEP/Light chains, autoimmune profile, Hepatitis/HIV testing
  - Paroviral PCR, Heavy metals: lead/copper
- Bone marrow biopsy and aspiration
  - Cytogenetics/ FISH/Iron/Reticulin stains
  - PNH testing
  - JAK-2 mutational testing
- Novel diagnostic tests
  - Mutation analysis

http://www.NCCN.org MDS Guidelines
http://www.hmds.org.uk/mds.html
MDS: Peripheral Smear
Hypogranular Hyosegmented neutrophil

Erythroid Dysplasia: Bone Marrow
Dyserythropoiesis

Granulocytic Dysplasia: Marrow and Blood
Dysgranulopoiesis
**Dysmegakaryopoiesis**

![Image](clinicaloptions.com/oncology)

Courtesy of Dr. Bennett and Dr. List.

**Bone Marrow Iron Stain: Ring Sideroblasts**

![Image](clinicaloptions.com/oncology)

**Deletion 5q Syndrome:**

- del(5q) as sole cytogenetic abnormality
- Female predominance (sex ratio: 7:3)
- Median age at diagnosis: 68 yrs
- Macrocytic anemia, mild leukopenia, normal or increased platelet count
- Indolent course, favorable prognosis
  - AML transformation: 12% to 16%
  - Median survival: > 5 yrs

MDS Classification: WHO 2008

- Refractory cytopenia with unilineage dysplasia (RCUD)
- Refractory anemia
- Refractory neutropenia
- Refractory thrombocytopenia
- Refractory anemia with ring sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Myelodysplastic syndrome with isolated del (5q)
- Refractory anemia with excess blasts (RAEB)
  - RAEB-1 (5-9% blasts in the bone marrow)
  - RAEB-2 (10-19% blasts in the bone marrow)

Provisional entity: Refractory anemia with ring sideroblasts with thrombocytosis: RARS-T

WHO Revisions 2008: MDS Cytogenetic Minimal Criteria

- Presence of a refractory cytopenia without morphologic features and the following cytogenetic abnormalities considered "presumptive evidence" of MDS:
  - Unbalanced
    - -7 or del(7q)
    - -5 or del(5q)
    - t(17q) or t(17p)
    - del(11q)
    - del(12p) or t(12p)
    - del(9q)
    - idic(X)(q13)
  - Balanced
    - t(11;16)(q23;p13.3)
    - t(3;21)(q26.2;q22.1)
    - t(1;3)(p36.3;q21.1)
    - t(2;11)(p21;q23)
    - inv(3)(q21;q26.2)
    - t(6;9)(p23;q34)
  - Other
    - Complex karyotype (3 or more abnormalities)

The International Prognostic Scoring System (IPSS)
A Tool for Risk Stratification

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>≥2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow blasts</td>
<td>&lt;5%</td>
<td>5% to 10%</td>
<td>11% to 20%</td>
<td>21% to 30%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Cytopenias†</td>
<td>0/1</td>
<td>2/3</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Total Score

<table>
<thead>
<tr>
<th>Risk</th>
<th>Low</th>
<th>Intermediate I</th>
<th>Intermediate II</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>5.7</td>
<td>3.5</td>
<td>1.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Good = normal, Y, del(5q), del(20q); intermediate = other karyotypic abnormalities; poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.
†Hb < 10 g/dL, ANC < 1800/μL, platelets < 100,000/μL.
Survival and AML progression according to IPSS


Revised IPSS

Design of the new Prognostic System

Revised IPSS

IPSS-R for MDS: Prognostic Score

Values *

Prognostic Risk Groups/Score

1. Very Good 0-2
2. Good 2-3
3. Intermediate 3-5
4. Poor 5-7
5. Very Poor 7-9

* Prognostic analysis for survival and AML evolution

www.MD-Congress.com
**Prognostic Model for Low-risk MDS**

<table>
<thead>
<tr>
<th>Adverse Factor</th>
<th>Coefficient</th>
<th>P Value</th>
<th>Assigned Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfavorable cytogenetics*</td>
<td>0.203</td>
<td>&lt; .0001</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 60 yrs</td>
<td>0.348</td>
<td>&lt; .0001</td>
<td>2</td>
</tr>
<tr>
<td>Hb &lt; 10 g/dL</td>
<td>0.216</td>
<td>&lt; .0001</td>
<td>1</td>
</tr>
<tr>
<td>Plt &lt; 50 x10^9/L</td>
<td>0.498</td>
<td>&lt; .0001</td>
<td>2</td>
</tr>
<tr>
<td>50-200 x10^9/L</td>
<td>0.277</td>
<td>.0001</td>
<td>1</td>
</tr>
<tr>
<td>BM blasts ≥ 5%</td>
<td>.0001</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*In this analysis, diploid and 5q were favorable cytogenetics, all others were considered as unfavorable cytogenetics.


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**Clinical Effect of Point Mutations in Myelodysplastic Syndromes**

Rafael Bejar, M.D., Ph.D., Kristen Stevenson, M.S., Omar Abdel-Wahab, M.D., Naomi Galili, Ph.D., Björn Nilsson, M.D., Ph.D., Guillermo Garcia-Manero, M.D., Hagop Kantarjian, M.D., Azra Raza, M.D., Ross L. Levine, M.D., Donna Neuberg, Sc.D., and Benjamin L. Ebert, M.D., Ph.D.

**ABSTRACT**
Point Mutations in MDS

- Of the 439 patients evaluated, 51% had at least 1 mutation
  - 52% of the patients with normal cytogenetics
- In a multivariable analysis that included clinical features and other mutations, TP53, EZH2, ETV6, RUNX1, and ASXL1 were shown to be predictive of survival independent of IPSS, age, and sex
  - 31% of patients had mutations in the 5 key genes

Frequency of Mutation and Association with Median Survival.

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>No. of Samples (%)</th>
<th>Median Survival (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples</td>
<td>430 (1.00)</td>
<td>1.88 (1.66-2.14)</td>
<td></td>
</tr>
<tr>
<td>TET2</td>
<td>90 (20.5)</td>
<td>2.06 (1.26-2.55)</td>
<td>0.48</td>
</tr>
<tr>
<td>ASXL1</td>
<td>63 (14.4)</td>
<td>1.73 (0.96-1.99)</td>
<td>0.063</td>
</tr>
<tr>
<td>RUNX1</td>
<td>39 (8.7)</td>
<td>1.18 (0.77-1.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TP53</td>
<td>33 (7.5)</td>
<td>0.85 (0.44-1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EZH2</td>
<td>26 (6.4)</td>
<td>0.79 (0.57-1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NRAS</td>
<td>10 (2.3)</td>
<td>1.03 (0.44-1.98)</td>
<td>0.006</td>
</tr>
<tr>
<td>JAK2</td>
<td>13 (3.0)</td>
<td>2.14 (1.02-3.12)</td>
<td>0.06</td>
</tr>
<tr>
<td>ETV6</td>
<td>12 (2.7)</td>
<td>0.83 (0.49-1.40)</td>
<td>0.35</td>
</tr>
<tr>
<td>CSL</td>
<td>10 (2.3)</td>
<td>1.02 (0.54-1.32)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

General Treatment Principles

- Individualize therapy (according to risk group, patient preference)
  - “To cure” approach:
    - Bone marrow transplantation: The only known curative modality, but appropriate/practical only in a small subset
  - Non-curative approaches:
    - Supportive care/ Chemotherapy
    - Decreased transfusion, infection, improvement in quality of life and prolongation of survival
Allogeneic SCT in MDS

- 452 pts Rx (89-97) by IBMTR for MDS
- Median age 38 yr (2-64)
- RA-RAS 40%; RAEB – RAEBT 60%

<table>
<thead>
<tr>
<th>Outcome</th>
<th>% at 3-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRM</td>
<td>37</td>
</tr>
<tr>
<td>Relapse</td>
<td>23</td>
</tr>
<tr>
<td>DFS</td>
<td>40</td>
</tr>
<tr>
<td>Survival</td>
<td>42</td>
</tr>
</tbody>
</table>


BMT for MDS patients
EBMT Experience: Results

- The 4-year estimate OS of the whole cohort was 31%

Anemia Management Algorithm 2012:
Low-/Intermediate-1 Risk MDS

- Epo < 500 mU/mL, < 2 U RBC/mo
- Epo > 500 mU/mL, RCDM ≥ 2 U RBC/mo

- ESA
- del(5q)
- Lenalidomide
- + GCSF
- HMA
- IST

**Case: Low Risk MDS**

- A 60-year-old man with easy bruising and shortness of breath
- CBC reveals the following
  - WBC: 3400 (ANC 1900)
  - Hgb: 8.0 g/dL, MCV: 98
  - Platelets: 177,000
  - Epo level: 175

- Bone marrow biopsy:
  - Hypercellular, with trilineage dysplasia, hypolobated megakaryocytes and 4% myeloblasts
  - Cytogenetic studies reveal normal cytogenetics

**Erythropoietin in MDS**

- Response rates to erythropoietin much lower in MDS than in other malignancies
  - Mean response rate: 16% to 20%
  - Predictors for good response were serum EPO level < 500 U/L, and lack of previous need for transfusion
- Response rates may improve when given in combination with G-CSF (> 40%), particularly in patients with RARS

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Ludwig H. Semin Oncol. 2002;29(3 suppl 8):45-54.

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**Erythropoietin + G-CSF in MDS: Patient Selection**

<table>
<thead>
<tr>
<th>Score</th>
<th>Treatment response criteria</th>
<th>Treatment response score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1</td>
<td>Stable Hgb &gt;11.5 g/dL, or total stop in RBC transf</td>
<td>eEPO &lt;100 U/L</td>
</tr>
<tr>
<td></td>
<td>Increase in Hgb with &gt;1.5 g/dL</td>
<td>100-500 U/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;500 U/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>U RBC/m</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22 units/m</td>
</tr>
<tr>
<td>1-2</td>
<td></td>
<td>Good response (74%, n=34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermediate response (33%, n=31)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>Poor response (7%, n=20)</td>
<td></td>
</tr>
</tbody>
</table>

Case Study

- A 58-yr-old white male has been referred to your office for evaluation of symptomatic anemia. His hemoglobin is low at 10 g/dL, with a normal MCV. WBC count is 6.5/μL and platelet count is 185,000/mm³. Serum ferritin is elevated to 630 ng/mL.
- A bone marrow biopsy and aspirate with cytogenetic testing is performed, revealing 1% blasts.
- Ten of 20 metaphases have an isolated chromosome 5q-deletion.
- Epo level is 615

Study MDS-003: Lenalidomide in MDS With Chromosome 5q Deletion

Eligibility:
- Del 5q-1
- RBC transfusion 2 U/ wk
- ≥60 wk transfusion
- ANC >3000/μL
- Platelets >200,000/μL
- De novo MDS
- IPSS Low/Mid-1 MDS

Primary endpoint: transfusion independence (Hgb ≥ 1 g/dL)
Secondary endpoints: cytogenetic response, pathologic response, safety

### EPO + G-CSF in MDS: Long-term Outcome

<table>
<thead>
<tr>
<th>Long-term follow-up in 3 Nordic MDS studies</th>
<th>Median Response Duration (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=123)</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>Complete responders (n=27)</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>Partial responders (n=41)</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Low/Nil (n=48)</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Int-2 (n=48)</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>FAB RA/RARS (n=48)</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>FAB RARS (n=48)</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Good PR (n=48)</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Int PR (n=48)</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Poor PR (n=48)</td>
<td></td>
<td>23</td>
</tr>
</tbody>
</table>

Compared with untreated patients from IPSS database, no difference was found in survival or AML evolution.
MDS-003: RBC Transfusion Independence in Del(5q) MDS

<table>
<thead>
<tr>
<th>Erythroid Response Rate (N=148)</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion Independence*</td>
<td>99 (67)</td>
<td>59–74</td>
</tr>
<tr>
<td>&lt;50% decrease in no. transfusions</td>
<td>13 (9 )</td>
<td>5–15</td>
</tr>
<tr>
<td>Total transfusion response</td>
<td>112 (76)</td>
<td>88–82</td>
</tr>
</tbody>
</table>

Transfusion Independence Response Characteristics

<table>
<thead>
<tr>
<th>Median Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to response (wk)</td>
</tr>
<tr>
<td>Hgb increase (g/dL)</td>
</tr>
</tbody>
</table>

*For ≥ 2 wk and ≥ 1 g/dL rise in Hgb
*From baseline to maximum Hgb during RBC transfusion independence


MDS-002: Lenalidomide in Non-del(5q) MDS

Eligibility
- IPSS diagnosed low/neutropenic MDS w/o del(5q) abnormality
- ≥ 2 U RBCs/8 wks
- Platelets > 50,000/µL
- ANC > 500/µL

Yes: Continue
No: Off study

Dose reduction
- 5 mg QD
- 5 mg QOD

Primary endpoint: Ti, Hb response
Secondary endpoints: cytogenetic response, safety
MDS-002: Response to Lenalidomide Therapy

- Erythroid Response:
  - TI: 56/214 (26%)
  - TI + Minor: 93/214 (43%)
- Cytogenetic Response:
  - CCR: 4/47 (9%)
  - CCR + PR: 9/47 (19%)

- Median Hb increase: 3.2 g/dL
- Time to response: 4.8 wks
- Median duration of response: 41 wks


MDS-002: Untransfused Hgb Values in Non-del(5q) Patients Receiving Lenalidomide

- Normalized, per NCCN guidelines

MDS-002/003: Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Grade ≥ 3 Adverse Events, %</th>
<th>Non-del(5q)</th>
<th>del(5q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25</td>
<td>55</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>


MDS-004 Trial Design

Double-blind phase: Len 5 mg vs PBO and Len 10 mg vs PBO

- Patients stratified by IPSS score and cytogenetic complexity prior to randomization.
- Bone marrow assessments were performed at baseline, 12 weeks, and every 24 weeks thereafter.
- ANC, absolute neutrophil count; IPSS, International Prognostic Scoring System; LEN, lenalidomide; MDS, myelodysplastic syndromes; PBO, placebo; RBC-TI, red blood cell transfusion independence.

Efficacy: RBC-TI and Hemoglobin Over Time (mITT Population)

- Consistent results were observed in the ITT population (N = 205).
- Achievement of RBC-TI for 126 weeks was not affected by age, gender, FAB classification, IPSS risk, time from diagnosis, cytogenetic complexity, baseline platelet count, or number of cytopenias at baseline.
- Hemoglobin increased over time with a maximum median change in responders of LEN 5 mg of 5.1 g/dL and LEN 10 mg of 9.1 g/dL.

mITT population defined as patients with complete confirmed MDS who received ≥ 1 dose (N = 129).
**Lenalidomide-Associated AML Progression and Death: Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lenalidomide Treated (n = 295)</th>
<th>Untreated (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-yr cumulative incidence, %</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>5-yr cumulative incidence, %</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Median time to AML progression, yrs</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-yr cumulative probability, %</td>
<td>90</td>
<td>74</td>
</tr>
<tr>
<td>5-yr cumulative probability, %</td>
<td>54</td>
<td>41</td>
</tr>
<tr>
<td>Median OS, yrs (95% CI)</td>
<td>5.2 (4.5-5.9)</td>
<td>3.8 (2.9-4.8)</td>
</tr>
</tbody>
</table>

- Factors associated with increased risk of AML progression: presence of > 1 cytogenetic abnormality in addition to del(5q), bone marrow blast percentage, and transfusion burden
- Factors associated with decreased risk of death: lenalidomide treatment, female sex, higher hemoglobin level, and higher platelet count


**Ineffective Hematopoiesis in MDS Immunopathogenesis**


**Relation Between Age and Response to IST**

Immunosuppressive Therapy (IST): Summary

- Age is the strongest variable for IST response\(^1\,^2\)
  - Pathogenetic difference in MDS of younger adults
- Responses are durable and may modify adverse effect of RBC-transfusion dependence on OS\(^1\)
- Karyotype may influence IST response and disease biology
  - Low frequency of IST response in del(5q)\(^1\)
  - High response rate in trisomy 8\(^3\)
  - NIH 8/17 (47%)
  - WT1 amplification with specific cellular response
  - Autoimmune hematopoietic suppression may select for +8 expansion


**CALGB 9221:** Randomized phase 3 study of Azacitidine in MDS

1. Supportive Care
   - Exit Criteria
     - Continue until Eopoint
   - Yes → Aza C
     - (dose as per arm #2)
   - No → Exit

2. Aza C75mg/m\(^2\)/d x 7 days q28 x 4

<table>
<thead>
<tr>
<th>M</th>
<th>0</th>
<th>29</th>
<th>57</th>
<th>113</th>
</tr>
</thead>
</table>

**Response**
- Continue Rx
- No Response → Off Study

**Patients characteristics:**

<table>
<thead>
<tr>
<th>MDS Subtype</th>
<th>RA</th>
<th>RARS</th>
<th>RAEB</th>
<th>RAEB-T</th>
<th>CMML</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>21.2%</td>
<td>8.1%</td>
<td>38.4%</td>
<td>16.2%</td>
<td>8.1%</td>
<td>10.1%</td>
</tr>
<tr>
<td>RARS</td>
<td>6.1%</td>
<td>5.5%</td>
<td>42.4%</td>
<td>15.2%</td>
<td>7.6%</td>
<td>9.8%</td>
</tr>
<tr>
<td>RAEB</td>
<td>38.4%</td>
<td>5.5%</td>
<td>42.4%</td>
<td>15.2%</td>
<td>7.6%</td>
<td>9.8%</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>16.2%</td>
<td>5.5%</td>
<td>42.4%</td>
<td>15.2%</td>
<td>7.6%</td>
<td>9.8%</td>
</tr>
<tr>
<td>CMML</td>
<td>8.1%</td>
<td>5.5%</td>
<td>42.4%</td>
<td>15.2%</td>
<td>7.6%</td>
<td>9.8%</td>
</tr>
<tr>
<td>AML</td>
<td>10.1%</td>
<td>5.5%</td>
<td>42.4%</td>
<td>15.2%</td>
<td>7.6%</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

Myelodysplastic Syndromes: Case-Based Workshops With the Experts

Study 9221: RBC Transfusion Independence

- Benefit extended across all MDS subtypes
- Median time to transfusion independence was ~2.5 months

Randomized Phase II Study of Alternative Azacitidine Dose Schedules

Eligibility
- All FAB
- Cytopenia
- ECOG PS: 0-3

Study Design (N = 151)

- 5-2-2: 75 mg/m² (n = 50)
- 5-2-5: 50 mg/m² (n = 51)
- 5: 75 mg/m² (n = 50)

12 Cycles
AZA x 5 days q4-6 wks

Alternate AzaC Dose Schedule Study: Frequency of Major HI in Evaluable Patients (N = 139)

<table>
<thead>
<tr>
<th>Lineage HI in Evaluable Pts.* n (%)</th>
<th>5-2-2 (n = 50)</th>
<th>5-2-5 (n = 51)</th>
<th>5d (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid MA</td>
<td>19/43 (44)</td>
<td>19/43 (44)</td>
<td>20/44 (46)</td>
</tr>
<tr>
<td>RBC-TI</td>
<td>12/24 (50)</td>
<td>12/22 (55)</td>
<td>15/25 (64)</td>
</tr>
<tr>
<td>Platelets MA</td>
<td>12/28 (43)</td>
<td>8/30 (27)</td>
<td>11/22 (50)</td>
</tr>
<tr>
<td>Any HI</td>
<td>22/50 (44)</td>
<td>23/51 (45)</td>
<td>28/50 (56)</td>
</tr>
<tr>
<td>Neutrophils MA</td>
<td>4/23 (17)</td>
<td>4/23 (17)</td>
<td>9/24 (38)</td>
</tr>
<tr>
<td>Heme AEs &gt; grade 3</td>
<td>33/50 (66)</td>
<td>24/48 (50)</td>
<td>17/50 (34)</td>
</tr>
<tr>
<td>AEs Tx delay</td>
<td>34/50 (68)</td>
<td>30/48 (63)</td>
<td>17/50 (34)</td>
</tr>
</tbody>
</table>

IWG 2000 HI criteria.
Hematologic Improvement

- Erythroid Major
- Platelet Major
- Neutrophil Major
- Any HI*

*Pts counted only once for best response in an improvement category
†Minor improvement at top of HI columns

Decitabine Phase 3

Demographics:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Decitabine (n = 89)</th>
<th>Supportive Care (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>59 (66)</td>
<td>57 (70)</td>
</tr>
<tr>
<td>Median Age</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Median Time From Diagnosis (months)</td>
<td>7.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Type of MDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De novo</td>
<td>77 (87)</td>
<td>70 (86)</td>
</tr>
<tr>
<td>Secondary</td>
<td>12 (13)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Previous MDS Therapy</td>
<td>20 (22)</td>
<td>16 (20)</td>
</tr>
<tr>
<td>IPSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>23 (26)</td>
<td>21 (26)</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>38 (43)</td>
<td>36 (44)</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>28 (31)</td>
<td>24 (30)</td>
</tr>
</tbody>
</table>


Response to Decitabine in Subgroups

<table>
<thead>
<tr>
<th>Overall Response Rate (CR+PR)*</th>
<th>Decitabine (n = 89)</th>
<th>Supportive Care (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS subgroups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>21%</td>
<td>0%</td>
</tr>
<tr>
<td>High Risk</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>Prior MDS Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>No</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>De novo MDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>No</td>
<td>16%</td>
<td>0%</td>
</tr>
</tbody>
</table>


Phase III Intergroup Study of Lenalidomide (LEN) vs LEN + Epoetin Alpha in Low/Int-1 MDS (ECOG 2905)

**Eligibility**
- HR: age ≥ 18 years
- IPSS Low/Int-1
- Hgb < 9.5 g/dL
- Poor EPO resp profile or failed EPO
- Stratify:
  - del(5q)
  - sEPO
  - Prior EPO/DA

**Principal Objective:**
- Modified IWG 2000 MER

**Secondary:**
- Time to MER; Duration of MER; LEN mechanism of action; Frequency of: MER to salvage combination therapy; cytogenetic response; hematologic response


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Phase 1 Dose-Ranging Study of Oral Ezatiostat Hydrochloride (Telintra®, TLK199) in Combination with Lenalidomide in Patients with Non-Del (5q) Low to Intermediate-1 Risk (MDS)

- In Low to Intermediate-1 (Int-1) risk non-del(5q) MDS, lenalidomide treatment is less effective with a lower response rate (25%) and shorter response duration
- Ezatiostat, a glutathione S-transferase P1-1 (GST P1-1) inhibitor, activates Jun kinase, promoting the growth and maturation of hematopoietic progenitors while inducing apoptosis in malignant cells.
- RP2D 2000 mg TLK/10 mg len
- Hi-E 43%, 36% RBC T1.

Raza et al. Blood 2011; 2278

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Romiplostim vs Placebo in Low- or Intermediate-1-Risk MDS

- Patients with low/IPSS Low or intermediate-1 MDS and low platelet count receiving supportive care (N = 250)
- 1:1 randomization
- Placebo weekly + Standard Care
- Patients with low/IPSS Low or intermediate-1 MDS and low platelet count receiving supportive care (N = 187)
- Placebo weekly
- **Primary endpoint:** clinically significant bleeding events (≥ grade 2 according to modified WHO scale)
- **Secondary endpoints:** platelet transfusion events, bleeding events, platelet response, OS, safety, progression to AML

Romiplostim MDS Study: Conclusions

- Use of romiplostim in patients with low-intermediate-1-risk MDS and low platelet counts yielded several benefits vs placebo
  - Platelet response increased 15-fold
  - Overall bleeding events significantly reduced
  - ≥ grade 2 bleeding events significantly decreased in patients with baseline platelet count ≥ 20,000 cells/mm³
  - Platelet transfusion events significantly decreased in overall population and in patients with baseline platelet count < 20,000 cells/mm³
- Romiplostim generally well tolerated, with toxicity profile similar to placebo
- Increases in blast counts and AML progression more frequent with romiplostim vs placebo, prompting study halt


Novel Agents/Trials in low risk MDS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial Phase</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>siltuximab</td>
<td>2</td>
<td>IL-6 antibody</td>
</tr>
<tr>
<td>Oral azacitidine</td>
<td>2</td>
<td>Hypomethylating agent</td>
</tr>
<tr>
<td>Telitra</td>
<td>2</td>
<td>GST inhibitor</td>
</tr>
<tr>
<td>LBH-689</td>
<td>2</td>
<td>HDAC inhibitor</td>
</tr>
<tr>
<td>Revlimid + Azacit</td>
<td>2</td>
<td>Combination trial/Rash</td>
</tr>
<tr>
<td>Eltrombopag</td>
<td>2</td>
<td>TPO Agonist</td>
</tr>
</tbody>
</table>

Conclusions & Recommendations:

MDS:
- Significant impact upon patient survival and quality of life

Treatment Directions:
- SCT is the only curative option.
- Several agents have already demonstrated a significant impact on survival.
- Several promising new agents are on the horizon, the results of trial evaluating such novel agents are on their way.
- Improvement in our understanding of disease biology is critical to continue to provide rationale therapeutic options to patients with this disease.