Advances in the Management of Myelodysplastic Syndromes

Southwestern Conference on Medicine
May 1, 2009

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Disclosures:

Celgene, Eisai, Bristol Myers Squibb
Methylgene, Novartis
TherEpi
CASE 1

60 year old retired high school chemistry teacher. Presents with a 3 month history of feeling “tired”.

WBC: 12.0
Hgb/Hct: 8.8/24.0
Plt: 191
CASE 1

What intervention would you recommend next?

A) Colonoscopy
B) Bone Marrow biopsy
C) Review of Peripheral Smear
D) A trial of iron replacement
CASE 2

76 year old retired oil worker with a past medical history of NHL (non-Hodgkin’s lymphoma) cured with CHOP chemotherapy. Patient has a routine CBC as part of an annual physical exam.

WBC: 12.0
Hgb/Hct: 8.8/24.0
MCV: 95
Plt: 56
CASE 2

What intervention would you recommend next?

A) Colonoscopy
B) Bone Marrow biopsy
C) Review of Peripheral Smear
D) A trial of iron replacement
Causes of anemia in elderly
Anemia* in the Elderly (Age ≥ 65 Years)

*Anemia was defined as < 13 g Hgb/dL for men and < 12 g Hgb/dL for women.
Adapted from Guralnik et al. Hematology. 2005;528-532, with permission.

*Anemia was defined as < 13 g Hgb/dL for men and < 12 g Hgb/dL for women.
Adapted from Guralnik et al. Hematology. 2005;528-532, with permission.
## Anemia in the Elderly (Age ≥ 65 Years) (cont)

<table>
<thead>
<tr>
<th>Type of Anemia</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss/nutrition related</td>
<td>34</td>
</tr>
<tr>
<td>Chronic illness/inflammation or chronic renal failure</td>
<td>32</td>
</tr>
<tr>
<td>Unexplained</td>
<td>34</td>
</tr>
</tbody>
</table>

- Unrecognized MDS may represent an important cause of *unexplained* anemia in the elderly

What is MDS?

Other names:
- Refractory anemia (1938)
- Preleukemia (1953)
- Smoldering leukemia (1963)
- Dysmyelopoietic anemia (1980)
- MDS (1982)

Clonal? Heterogeneous? Myeloid?
The Myelodysplastic Syndromes
Epidemiology

• 15,000 new cases/year in US (Adults)
• More common than AML
• Median Survival 1-3 years
• Predominantly a disease of the elderly
  – Median age > 60
  – Greater incidence in males than females
  – Incidence increases with age

Etiology of MDS

- benzene or toluene
- gasoline or diesel (?)
- pesticides (?)
- virus (?)
- genetic (?)
- secondary to chemotherapy with or without radiation therapy
Probability of Treatment-related MDS (tMDS) After Autologous Transplantation for NHL

Differential Diagnosis of MDS

- nutritional deficiencies
- heavy metal poisoning
- alcoholism
- metabolic disturbances
- chronic inflammation
- Tuberculosis

- liver disorders
- hypersplenism
- Hodgkin’s disease
- metastatic carcinoma
- recent chemotherapy
The Myelodysplastic Syndromes
Overview

• Clonal disorder characterized by hypercellular marrows, peripheral cytopenias, and cell functional abnormalities

• Dominant feature: Ineffective hematopoiesis with peripheral blood cytopenias

• Bone marrow failure
  – Majority succumb to infection or bleeding
  – Transformation to acute leukemia in 35-40% range

• High mortality rate

• Supportive Care has been the standard treatment

Clinical Presentation

- Half of patients are >70 years old
- Half of patients have no symptoms related to MDS
- Most common symptoms are those from anemia
- A few patients have symptoms of bleeding or infection
- Physical findings are unusual; splenomegaly found in <20%
- Some patients present with fever
Age-Related Incidence of MDS

Age-Specific Incidence Rates (per 100,000), Years

- <50: 0.5
- 50-59: 5.3
- 60-69: 15
- 70-79: 49
- 80 and over: 89

Age in 5-Year Blocks

# MDS FAB Classification

<table>
<thead>
<tr>
<th>Category</th>
<th>% Blasts in Bone Marrow</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA (Refractory Anemia)</td>
<td>&lt;5%</td>
<td>19-64</td>
</tr>
<tr>
<td>RARS (Refractory Anemia with Ringed Sideroblasts)</td>
<td>&lt;5%</td>
<td>21-76</td>
</tr>
<tr>
<td>RAEB (Refractory Anemia with Excessive Blasts)</td>
<td>5%-20%</td>
<td>7-15</td>
</tr>
<tr>
<td>RAEB-T (Refractory Anemia with Excessive Blasts in transformation)</td>
<td>21%-30%</td>
<td>5-12</td>
</tr>
<tr>
<td>CMML (Chronic Myelomonocytic Leukemia)</td>
<td>1%-20%</td>
<td>8-60+</td>
</tr>
</tbody>
</table>

## 5q- Syndrome

**Hematologic Features**

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>43</td>
</tr>
<tr>
<td>Female predominance</td>
<td>29 (67)</td>
</tr>
<tr>
<td>Platelets &gt; 150,000/µL</td>
<td>36 (84)</td>
</tr>
<tr>
<td>Dysplastic megakaryocytes</td>
<td>40 (92)</td>
</tr>
<tr>
<td>Erythroid hypoplasia</td>
<td>38 (90)</td>
</tr>
<tr>
<td>Leukemia evolution</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Median survival*</td>
<td>&gt;5 years</td>
</tr>
</tbody>
</table>

*Cancer Genet Cytogenetics 1985; 17: 189.*

*IPSS.*
Evolution of MDS Classification Systems

- FAB 1976, 1982
  - Based on morphology, survival, and blast number

- WHO 1997, 2001
  - Based on morphology, survival, and blast number

- IPSS 1997
  - Based on time to AML, % blasts, karyotype, # of cytopenias

- WPSS 2005
  - Based on WHO morphology, transfusion requirements, IPSS cytogenetic risk
WHO Classification

MDS
- RA
  - RA
  - RCMD
- RARS
  - RARS
  - RCMD-RS
- RAEB
  - RAEB I (5-10% Blasts)
  - RAEB II (11-19% Blasts)
- Other
  - 5q- Syndrome
  - MDS-U

MDS/MPD
- CMML (>13,000/µL)
- JMML

AML
- >20% Blasts
- RAEB-t
# IPSS Scoring System

- All 3 prognostic variables are required to generate IPSS score

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow Blasts</td>
<td>&lt;5%</td>
</tr>
<tr>
<td></td>
<td>5%-10%</td>
</tr>
<tr>
<td></td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>11%-20%</td>
</tr>
<tr>
<td></td>
<td>21%-30%</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td>Cytopenias†</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td>2/3</td>
</tr>
</tbody>
</table>

*Good = normal, -Y, del(5q), del(20q);
Intermediate = other karyotypic abnormalities;
Poor = complex (≥3 abnormalities) or chromosome 7 abnormalities.

†Hgb <10 g/dL; ANC <1800/µL; platelets <100,000/µL.

RISK: LOW (0), INT-1 (0.5-1.0), INT-2 (1.5-2.0), HIGH (≥ 2.5)

# Survival: MDS vs. Lung Cancer

<table>
<thead>
<tr>
<th>IPSS Score</th>
<th>Risk Group</th>
<th>Median Survival (Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>5.7</td>
</tr>
<tr>
<td>0.5-1</td>
<td>Int-1</td>
<td>3.5</td>
</tr>
<tr>
<td>1.5-2</td>
<td>Int-2</td>
<td>1.2</td>
</tr>
<tr>
<td>&gt;2</td>
<td>High</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Supportive Care

Includes:

- Transfusions
- Antibiotics
- Chelation agents
- Growth factors
  - EPO +/- G-CSF (or GM-CSF)
  - Treatment with growth factors (EPO + G-CSF) have not demonstrated improvement in survival and/or reduced risk of transformation to AML in MDS patients

EPO=erythropoietin; G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte macrophage colony-stimulating factor.

Erythropoietin + G-CSF in MDS: Patient Selection


**Good response** (74%, n=34)

**Intermediate response** (23%, n=31)

**Poor response** (7%, n=29)

**RA, RARS, RAEB**

**Score > +1**

**Score –1 to +1**

**Score < –1**

*Treatment response score*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>s-epo U/L</td>
<td>&lt;100</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>100–500</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>&gt;500</td>
<td>–3</td>
</tr>
<tr>
<td>Transf</td>
<td>&lt;2 units/m</td>
<td>+2</td>
</tr>
<tr>
<td>U RBC/m</td>
<td>= or &gt;2 units/m</td>
<td>–2</td>
</tr>
</tbody>
</table>
RBC Transfusions

• Majority of patients will require transfusion support
  – Thresholds based on symptoms and comorbidities, not just hemoglobin level

• Multiple transfusions lead to complications
  – Allo-sensitization
  – Iron overload
    • Iron chelation for 20-30 units pRBC and prolonged life expectancy
      – Oral agent (deferasirox) role unknown in MDS
    • Increased iron absorption may be seen in RARS

http://www.NCCN.org MDS Guidelines
Deferasirox Study: Reduction in Ferritin During Study

Absolute Ferritin Levels

Deferasirox Study: Unanswered Questions

- Does iron chelation improve survival in MDS?
  - Would require lengthy, controlled study

- Does iron chelation prevent clinical complications in MDS, as it does in congenital anemias?
  - Issues may be distinct for heart vs liver

- In which patient groups is iron chelation cost-effective?

- What is the long-term safety and efficacy profile of deferasirox?

MDS Treatment Approaches
Relapse-free Survival
Targeted busulfan and cyclophosphamide (tBuCy)

### Approximation of Life Expectancy (Years)

<table>
<thead>
<tr>
<th></th>
<th>Immediate Transplant</th>
<th>Transplant in 2 Years</th>
<th>Transplant at Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>6.51</td>
<td>6.86</td>
<td>7.21</td>
</tr>
<tr>
<td>Int-1</td>
<td>4.61</td>
<td>4.74</td>
<td>5.16</td>
</tr>
<tr>
<td>Int-2</td>
<td>4.93</td>
<td>3.21</td>
<td>2.84</td>
</tr>
<tr>
<td>High</td>
<td>3.20</td>
<td>2.75</td>
<td>2.75</td>
</tr>
</tbody>
</table>

The Decision

% Survival vs Time

HCT
No HCT

## Available Agents: Indications, Dosing, and MOA

<table>
<thead>
<tr>
<th></th>
<th>Azacitidine</th>
<th>Lenalidomide</th>
<th>Decitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>All MDS subtypes (FAB classes) <em>(IPSS: Low, Int-1, Int-2, High)</em></td>
<td>Low-risk MDS (IPSS low or Int-1) with deletion 5q; Transfusion dependent</td>
<td>All MDS subtypes (FAB classes) IPSS: Int-1, Int-2, High Secondary MDS</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>Subcutaneous Intravenous</td>
<td>Oral</td>
<td>Intravenous infusion (1–3 h)</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>75 mg/m²/d x 7 d q 4 wk</td>
<td>10 mg/d</td>
<td>45 mg/m²/d x 3 d q 6 wk</td>
</tr>
<tr>
<td><strong>MOA</strong></td>
<td>DNA hypomethylation</td>
<td>Immune modulation; angiogenesis inhibition</td>
<td>DNA hypomethylation</td>
</tr>
</tbody>
</table>

FAB = French-American-British; IPSS = International Prognostic Scoring System.


Genetics and DNA: “The Code of Life”

- DNA: the molecule of life
- Trillions of cells
- Each cell:
  - 46 human chromosomes
  - 2 m of DNA
  - 3 billion DNA subunits (the bases: A, T, C, G)
  - 80,000 genes code for proteins that perform all life functions
- Protein

- Cell
- Chromosomes
- Gene
“Genetics and Epigenetics”

The Phillips Sisters: “Ann Landers” and “Dear Abby”

Epigenetics = “Heritable Information not coded for in the DNA Sequence”
How are genes turned off? 
.... DNA Methylation

“ON”

Gene

DNA

RNA

Protein

Protein

Epigenetics in Cancer

DNA

Tumor Suppressor

Oncogene
How DNA Methyltransferase Inhibitors Work
Study 9221: A Randomized Phase III Controlled Trial of Subcutaneous VIDAZA® (azacitididine for injection) in MDS

- Minimum duration of supportive care=4 months unless transformation to AML; death or platelets <20 x 10^9/L at week 8 or later
- Growth factors were prohibited

BM=bone marrow.

## Analysis of Response

<table>
<thead>
<tr>
<th></th>
<th>SC</th>
<th>AZA</th>
<th>Crossover</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. Evaluated</strong></td>
<td>92</td>
<td>99</td>
<td>49</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>0 (0%)</td>
<td>7 (7%)*</td>
<td>5 (10%)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>0 (0%)</td>
<td>15 (16%) **</td>
<td>2 (4%)</td>
</tr>
<tr>
<td><strong>Improved</strong></td>
<td>5 (5%)</td>
<td>38 (37%) **</td>
<td>16 (36%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5 (5%)</td>
<td>60 (60%) **</td>
<td>23 (47%)</td>
</tr>
</tbody>
</table>

**P - value**  
* < 0.01  
**<0.001

Silverman L, et al. Randomized Controlled Trial of Azacitidine in Patients with MDS: A Study of the CALGB  
Study 9221: Time to Response

• The initial positive effect observed included:*
  – HgB (18.8%)
  – Platelets (25%)
  – WBC (18.8%)
  – Blasts (37.5%)

* Includes patients with adjudicated baseline diagnosis of AML

*Initial positive effect was defined as the first day of achievement of target for 4 weeks for at least one abnormality.

VIDAZA full prescribing information.
Data on file, Pharmion Corporation.
Azacitidine Treatment Prolongs Overall Survival in Higher-Risk MDS Patients Compared with Conventional Care Regimens: Results of the AZA-001 Phase III Study

P Fenaux, MD, GJ Mufti, MD, V Santini, MD, C Finelli, MD, A Giagounidis, MD, R Schoch, MD, A List, MD, S Gore, MD, J Seymour, MD, E Hellstrom-Lindberg, MD, J Bennett, MD, J Byrd, MD, J Backstrom, MD, L Zimmerman, BSN, D McKenzie, MS, CL Beach, PharmD and L Silverman, MD on behalf of the International Vidaza High-Risk MDS Survival Study Group
Azacitidine Survival Study

AZA 75 mg/m²/d x 7 d q28 d

Screening/Central Pathology Review

Investigator CCR Tx Selection

Randomization

• Best Supportive Care (BSC) only
• Low Dose Ara-C (LDAC, 20 mg/m²/d x 14 d q28-42 d)
• Std Chemo (7 + 3)

BSC was included with each arm
Tx continued until unacceptable toxicity or AML transformation or disease progression
Overall Survival: Azacitidine vs CCR
ITT Population

Log-Rank  p=0.0001
HR = 0.58 [95% CI: 0.43, 0.77]
Deaths: AZA = 82, CCR = 113
Difference: 9.4 months
# Secondary Endpoints: IWG (2000) RR and HI

## CCR Regimens

<table>
<thead>
<tr>
<th>Response</th>
<th>AZA N=179 (%)</th>
<th>CCR N=179 (%)</th>
<th>BSC Only N=105 (%)</th>
<th>LDAC N=49 (%)</th>
<th>Std Chemo N=25 (%)</th>
<th>P-Value AZA vs CCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (CR+PR)</td>
<td>29</td>
<td>12</td>
<td>5</td>
<td>12</td>
<td>40</td>
<td>0.0001</td>
</tr>
<tr>
<td>CR</td>
<td>17</td>
<td>8</td>
<td>1</td>
<td>8</td>
<td>36</td>
<td>0.02</td>
</tr>
<tr>
<td>PR</td>
<td>12</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>0.009</td>
</tr>
</tbody>
</table>

## IWG HI

<table>
<thead>
<tr>
<th></th>
<th>Major+Minor</th>
<th>HI-E Major</th>
<th>HI-P Major</th>
<th>HI-N Major</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>49</td>
<td>40</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>11</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>8</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>10</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>22</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0003</td>
<td>0.87</td>
</tr>
</tbody>
</table>
# Additional Analysis: Median OS by Investigator Selection

<table>
<thead>
<tr>
<th>Treatment</th>
<th>K-M OS Time mos</th>
<th>K-M OS Time mos</th>
<th>Hazard Ratio</th>
<th>Log-rank P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA (N=117) vs BSC (N=105)</td>
<td>21.1</td>
<td>11.5</td>
<td>9.6</td>
<td>0.56</td>
</tr>
<tr>
<td>AZA (N=45) vs LDAC (N=49)</td>
<td>24.5</td>
<td>15.3</td>
<td>9.2</td>
<td>0.58</td>
</tr>
<tr>
<td>AZA (N=17) vs Stand Chemo (N=25)</td>
<td>25.1</td>
<td>15.7</td>
<td>9.4</td>
<td>0.87</td>
</tr>
</tbody>
</table>
Azacitidine extends overall survival (OS) in higher-risk MDS without the necessity for complete remission

Alan List, Pierre Fenaux, Ghulam Mufti, Eva Hellstrom-Lindberg, Steven Gore, John Bennett, Lewis Silverman, Jay Backstrom, and CL Beach on behalf of the International Vidaza High-Risk MDS Survival Study Group

ASCO 2008
OS with AZA by Best Response (IWG 2000)

Proportion Surviving

Time (months) from Randomization

HI
78.4% (p<0.0001)
71.7% (p<0.0001)
67.5% (p=0.006)
41.3% (p=0.041)
26.2%

SD
CCR
DP
PR
CR
Azacitidine
5-azacytidine

Decitabine
5-aza-2'-deoxycytidine

RNA

DNA
Cytidine Analogs

Decitabine
Azacitidine
Cytarabine
Gemcitabine
Decitabine Phase 3 Study Design

- Open-label, 1:1 randomized, multi-center study in the US and Canada

Eligible Patients (n = 170)

- Decitabine + Supportive Care* (n = 89)
- Supportive Care* (n = 81)

Stratification
- IPSS Classification
- Prior Chemotherapy
- Study Center

*Antibiotics, Growth Factors and/or Transfusions


Study D-0007
Decitabine Phase 3
Dose and Administration

Schedule: 3 hour infusion q 8 hrs x 3 days

15 mg/m²
3 hour
8 hours

15 mg/m²
3 hour
8 hours

15 mg/m²
3 hour
8 hours

Three Consecutive Days

135 mg/m²
3 days
6 week cycle

Median number of cycles/patient: 3 (Range = 0 - 9)


Study D-9007
### Decitabine Phase III MDS Trial Results

<table>
<thead>
<tr>
<th>ITT Analysis</th>
<th>Decitabine* (N=89)</th>
<th>Supportive Care (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response (IWG Criteria)†</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>Complete Response</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Hematologic Improvement (IWG)</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>Overall Clinical Benefit (CR + PR + Hematologic Improvement)</td>
<td>30%</td>
<td>7%</td>
</tr>
<tr>
<td>Median Time to Response (CR + PR)</td>
<td>93d (55-272)</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Median Duration of Response (CR + PR)</td>
<td>288d (116-388)</td>
<td>Not assessed</td>
</tr>
</tbody>
</table>

*FDA approval based on response analysis; decitabine treatment did not significantly delay the median time to AML or death versus supportive care.

†P<0.001.

Decitabine Exposure in Phase 2 and 3 Studies

<table>
<thead>
<tr>
<th></th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>91-01</td>
<td>95-11</td>
</tr>
<tr>
<td>N</td>
<td>29</td>
<td>66</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>13 (45%)</td>
<td>17 (26%)</td>
</tr>
<tr>
<td>CR</td>
<td>8 (28%)</td>
<td>14 (21%)</td>
</tr>
<tr>
<td>PR</td>
<td>5 (17%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Median # cycles</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Multiple cycles of decitabine therapy may be required for optimal response

Survival and Efficacy of Decitabine in Myelodysplastic Syndromes (MDS), Analysis of the 5-Day IV Dosing Regimen

ASH 2007 Abstract #115

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Patients with intermediate-1, -2, or high-risk MDS or CMML + leukocytosis; performance status 0-2

(N = 124)

Decitabine 20 mg/m² IV over 1 hr daily for 5 days*
(n = 93)

Decitabine 20 mg/m² SQ daily for 5 days*
(n = 14)

Decitabine 10 mg/m² IV over 1 hr daily for 10 days*
(n = 17)

*Every 4 weeks up to 24 courses.
Comparison of outcome and side effects by dose schedule

<table>
<thead>
<tr>
<th>Parameter</th>
<th>5 Day IV</th>
<th>5 Day SQ</th>
<th>10 Day IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>64</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>CR / treated (%)</td>
<td>25 (39)</td>
<td>3 (21)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Median no. courses</td>
<td>5</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Median duration of therapy in mos (range)</td>
<td>5.4 (1.0 – 20.4+)</td>
<td>9.7 (0.5 – 22.9+)</td>
<td>10.8 (1.9 – 17.7+)</td>
</tr>
<tr>
<td>Median days to granulocytes recovery*</td>
<td>24</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>Median days to platelet recovery†</td>
<td>20</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>Median days to delivery of subsequent courses</td>
<td>35</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>No. courses requiring hospitalization (%)</td>
<td>50 (12)</td>
<td>14 (14)</td>
<td>23 (23)</td>
</tr>
</tbody>
</table>

Decitabine Survival vs Intensive Chemotherapy in Higher Risk MDS (Matched Group)


Survival

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Dead</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decitabine</td>
<td>124</td>
<td>82</td>
<td>20</td>
</tr>
<tr>
<td>Matched int. chemo.</td>
<td>115</td>
<td>87</td>
<td>12</td>
</tr>
</tbody>
</table>

p = 0.001
“A Silver Lining from Tragedy…”
Lenalidomide: Pharmacologic Evolution

Thalidomide  Lenalidomide

- More “potent” immunomodulator than thalidomide
  - Up to 50,000 times more potent inhibitor of TNFα
  - Increased stimulation of T-cell proliferation
  - Augmented stimulation of IL-2 and IFNγ production

Stirling D. Semin Oncol. 2001;28:602
Study MDS-003: Lenalidomide in MDS With Chromosome 5q Deletion

**Eligibility**
- del 5q31.1
- RBC transfusion ≥2 U/8 wk
- 16-wk transfusion Hx
- ANC >500/μL
- Platelets >50,000/μL
- de novo MDS
- IPSS Low/Int-1 MDS

**LENALIDOMIDE**
- 10 mg po × 21/28 days
- 10 mg po qd

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

# 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>≥50% decrease in no. of transfusions</td>
<td>13 (9)</td>
<td>5–15</td>
</tr>
<tr>
<td>Total transfusion response</td>
<td>112 (76)</td>
<td>68–82</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transfusion Independence Response Characteristics</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to response (wk)</td>
<td>4.6</td>
<td>1–49</td>
</tr>
<tr>
<td>Hgb increase† (g/dL)</td>
<td>5.4</td>
<td>1.1–11.4</td>
</tr>
</tbody>
</table>

*For ≥8 wk and ≥1-g/dL rise in Hgb
†From baseline to maximum Hgb during RBC transfusion independence

Questions?

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www.mds-foundation.org