Advances in MDS Treatment: What’s on the Horizon?
Mikael A. Sekeres, MD, MS
Professor of Medicine
Director, Leukemia Program

Outline

• MDS Overview
  • Treatment of Lower-risk Disease
  • Treatment of Higher-risk Disease

Current Risk Stratification (Greenberg P et al 2012)

<table>
<thead>
<tr>
<th>Cytogenetic risk group</th>
<th>Categories and Associated Scores</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>40.8</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(5q), del(12p) alone</td>
<td>48.6</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+del(5q), +del(12p)</td>
<td>20.5</td>
</tr>
<tr>
<td>Poor</td>
<td>del(5q), -7, double with del(7q)</td>
<td>15.8</td>
</tr>
<tr>
<td>Very poor</td>
<td>Complex with &gt; 3 abnormalities</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Recurrent Genetic Mutations in MDS

~90% of patients have a mutation detectable by current sequencing platforms

Mutations Influence Prognosis by IPSS Group

Analysis of Combined Datasets from the International Working Group for MDS-Molecular Prognosis Committee

Abstract # 907 Somatic Mutations in MDS Are Associated with Clinical Features and Predict Prognosis Independent of the IPSS-R

On behalf of the IWG for MDS investigators
The Revised International Prognostic Scoring System "Molecular" (IPSS-Rm)
A Validated and Dynamic Model in Treated Patients with Myelodysplastic Syndromes (MDS)


Leukemia Program and Translational Hematology and Oncology Research Department
Cleveland Clinic, Taussig Cancer Institute
Cleveland, Ohio

Clinical Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Training No.</th>
<th>Validation No.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>333</td>
<td>175</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>68 (20 – 87)</td>
<td>69 (25-86)</td>
<td>.36</td>
</tr>
<tr>
<td>Gender, Men</td>
<td>205 (62)</td>
<td>109 (63)</td>
<td>.32</td>
</tr>
</tbody>
</table>

Clinical Variables

- Median WBC, 10^9/L: 3.8 (1.6 – 11.8) vs. 5.2 (3.7 – 17.2) (p = .002)
- Median ANC, 10^9/L: 1.8 (1.0 – 2.9) vs. 2.6 (1.1 – 4.5) (p = .01)
- Median Hb, g/dL: 9.7 (7.9 – 13.4) vs. 8.8 (5.0 – 15.7) (p = .01)
- Median Platelets, 10^9/L: 100 (8 – 267) vs. 103 (23 – 297) (p = .04)
- Median BM Blast %: 2.5 (0 – 19) vs. 2.5 (0 – 19) (p = .09)

IPSS-R Category

- Very low: 13 (34) vs. 34 (19) (p = .04)
- Low: 37 (73) vs. 73 (42) (p = .02)
- Intermediate: 20 (26) vs. 26 (21) (p = .12)
- High: 17 (21) vs. 21 (12) (p = .08)
- Very high: 13 (11) vs. 11 (8) (p = .08)

Nazha et al. ASH 2015 [Abstract # 607] @AzizNazhaMD

Overall Survival by Mutated Gene

Univariate Hazard Ratios and 95% confidence intervals

IPSS-R Adjusted Hazard Ratios and intervals

Final Multivariable Survival Model

Hazard Ratio (95% CI)

<table>
<thead>
<tr>
<th>Mutated Genes [vs. Unmutated]</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>2.00</td>
<td>.0005</td>
</tr>
<tr>
<td>RUNX1</td>
<td>1.31</td>
<td>.0002</td>
</tr>
<tr>
<td>EZH2</td>
<td>1.30</td>
<td>.0005</td>
</tr>
<tr>
<td>ASXL1</td>
<td>2.01</td>
<td>.0205</td>
</tr>
<tr>
<td>SF3B1</td>
<td>1.19</td>
<td>.5182</td>
</tr>
<tr>
<td>CBL</td>
<td>1.11</td>
<td>.3344</td>
</tr>
<tr>
<td>U2AF1</td>
<td>1.17</td>
<td>.3632</td>
</tr>
<tr>
<td>TP53</td>
<td>1.2</td>
<td>.5486</td>
</tr>
</tbody>
</table>

Overall by Mutated Number

17 genes sequenced in 1996 patients with OS data

Overall Survival by Number

<table>
<thead>
<tr>
<th>Mutation Number</th>
<th>Number of Mutated Genes</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 (n=377)</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>1 (n=48)</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>2 (n=64)</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>4 (n=134)</td>
<td>66</td>
</tr>
<tr>
<td>5-6-7</td>
<td>6 (n=22)</td>
<td>60</td>
</tr>
<tr>
<td>SF3B1 only</td>
<td>207</td>
<td>65</td>
</tr>
</tbody>
</table>

Methods: IWG-PM MDS Sample Compilation

MDS sample data collected from 18 centers in Europe, the United States, and Asia

Clinical Features
- age and sex
- blast %
- karyotype
- hemoglobin
- platelet count
- neutrophil count

Overall Survival Data:
- available for 3359 patients
- 3.6 years follow-up
- 1780 deaths
- median OS 2.65 years

Data Summary

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Training No. / Validation No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Features</td>
<td>Age and sex, blast %, karyotype, hemoglobin, platelet count, neutrophil count</td>
</tr>
</tbody>
</table>

Treatment Status

Gene Mutations

18 MDS sample data collected from 18 centers in Europe, the United States, and Asia

Graphs and tables showing data and survival analysis.
Conclusions

- We developed a modification of IPSS-R that incorporates mutational data and enhances its predictive ability in MDS

- IPSS-Rm
  - Validated in a separate cohort
  - Dynamic (validated in paired sample cohorts)
  - Can be used in primary/secondary MDS and CMML regardless of initial of subsequent treatment
• MDS Overview
• Treatment of Lower-risk Disease
• Treatment of Higher-risk Disease

Abstract # 94 Low-Dose Hypomethylating Agents Are Effective in Patients with Low- or Intermediate-1-Risk Myelodysplastic Syndrome: A Report on Behalf of the MDS Clinical Research Consortium

Short N1, Garcia-Manero G1, Montalban Bravo G1, Sasaki K1, Sekeres M2, Komrokji R3, Steensma D4, DeZern A5, Roboz G6, Kadia T1, Borthakur G1, DiNardo C1, Miller D1, Estrov Z1, Pemmaraju N1, Daver N1, Verstovsek S1, Kantarjian H1, Jabbour E1

1The University of Texas MD Anderson Cancer Center, Houston, TX; 2Cleveland Clinic, Cleveland, OH; 3Moffitt Cancer Center, Tampa, FL; 4Dana-Farber Cancer Institute, Boston, MA; 5Johns Hopkins University, Baltimore, MD; 6Cornell Medical College, New York, NY

Low-dose HMAs in LR-MDS:

Eligibility

• Adult pts with de novo or secondary IPSS low- or intermediate-1-risk MDS, including CMML
• PS ≤ 3
• Normal organ function
• No prior HMA therapy

Response assessment by modified IWG 2006
• Between 11/2012 and 10/2015, 91 pts with LR-MDS treated and evaluable for response
• Median duration of follow-up = 14 months (range: 2-30 months)

<table>
<thead>
<tr>
<th>Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>33 (36)</td>
</tr>
<tr>
<td>mCR</td>
<td>8 (9)</td>
</tr>
<tr>
<td>HI</td>
<td>13 (14)</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>54 (59)</td>
</tr>
<tr>
<td>SD</td>
<td>31 (34)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (7)</td>
</tr>
</tbody>
</table>
Low-dose HMAS in LR-MDS: Conclusions

- Low-dose HMA therapy safe and effective in LR-MDS:
  - ORR: 59%
  - Transfusion independence rate: 32%
  - 1-year EFS rate: 62%
  - 1-year OS rate: 86%
- Randomized trial of low-dose AZA vs. DAC vs. best supportive care ongoing

Luspatercept Lower-Risk MDS Phase 2 Extension Study

A phase 2, multicenter, open-label, 3-month dose escalation study in adults with lower-risk MDS, followed by a 24-month extension study

- Eligibility
  - EPO >500 U/L or ESA refractory/intolerant/unavailable
  - No prior azacitidine or decitabine
  - No current ESA, G-CSF, GM-CSF, lenalidomide
- Efficacy endpoints (extension study)
  - LTB: Low transfusion burden patients (< 4 Units/8 wk, HB < 10 g/dL)
  - IWG HI-E: HB increase ≥ 1.5 g/dL for 8 weeks
  - HTB: High transfusion burden patients (≥ 4 Units/8 wk)
  - IWG HI-E: 24 Unit decrease Units over 8 weeks
- Other efficacy endpoints
  - RBC-TI: RBC transfusion independence ≥ 8 weeks
  - Time to/duration of HI-E response
  - HI-N, HI-P, HR-QoL (FACT-An), PD and iron biomarkers

Response Rates by Baseline Characteristics

- Majority of patients in extension study were RS+: ≥ 50% patients responded to luspatercept who had EPO up to 500 U/L or prior ESA treatment

Conclusions

- Lower risk MDS patients treated with luspatercept demonstrated a robust hematologic improvement per IWG HI-E and reduced transfusion burden
- Luspatercept was generally safe and well-tolerated
- Treatment for up to 1 year demonstrated sustained increases in hemoglobin and prolonged transfusion independence
- Patients who were refractory to prior ESA or had serum EPO up to 500 U/L responded particularly well to luspatercept treatment
- These results support the initiation of Phase 3 studies of luspatercept in patients with lower-risk MDS (MEDALIST)
Main Inclusion criteria:

- PLT count <30 G/L
- Ineligible or relapsed or refractory to receive other treatment options
- ESAs or G-CSF allowed during the study as per accepted standards.
- ECOG Performance Status 0-3
- Adequate baseline organ function

Main Exclusion criteria:

- WHO bleeding grade ≥ 2

Study design

Randomization 2:1

<table>
<thead>
<tr>
<th>Patients (N = 174)</th>
<th>CR and R</th>
<th>Placebo + Standard care (n = 58)</th>
<th>Eltrombopag + Standard care (n = 116)</th>
</tr>
</thead>
</table>

Dose start: 50 mg with increases every 2 weeks up to 300 mg daily.

Platelet responses

Time to Response (TTR):

- Eltrombopag: median 14 (IQR 8-39) days
- Placebo: median 85 (IQR 41-193) days (p = 0.023) *

Median daily eltrombopag dose at response: 50 (IQR 50-150) mg.

CONCLUSIONS

In patients with low and intermediate-1 risk MDS with severe thrombocytopenia, eltrombopag

- Is manageable with a low toxicity profile
- Raises PLT counts and induces durable PLT responses
- Is not associated with progression or AML evolution
- May be associated with remission
- Is associated with improvements in QoL in responsive patients

This ongoing trial will evaluate long-term safety of eltrombopag and its impact on survival.

Outline

- MDS Overview/Case
- Treatment of Lower-risk Disease
- Treatment of Higher-risk Disease
What happens when we add drugs together?

Aza + Pracinostat in MDS: Study Design
- Intermediate Risk-2 or High Risk MDS Patients
- Previously Untreated with HMA

- 102 evaluable patients: one-to-one randomization
- Primary analysis population defined as all randomized and treated patients
- Randomization stratified by IPSS risk group with a planned sample size of 100
- 24 sites in the U.S. activated, 19 sites enrolled patients
- FPI: June 17, 2013; LPI: Aug 29, 2014

Aza + Pracinostat in MDS: Inclusion Criteria
- Age ≥18 years
- Morphological diagnosis of MDS (any FAB subtype int-2 or high risk) per IPSS
- Previously untreated with hypomethylating agents
- Peripheral WBC count of <20,000 /μL
- ECOG Performance status ≤2
- Adequate organ function

Abstract #911: A Randomized, Placebo-Controlled, Phase II Study of Pracinostat in Combination with Azacitidine (AZA) in Patients with Previously Untreated Myelodysplastic Syndrome (MDS)

Guillermo Garcia-Manero, MD, Jesus G. Bardeja, MD, Rami S. Komrokji, MD, James Essell, MD, Roger M. Lyons, MD, Michael Maris, MD, Amy E. DeZern, MD, MHS, Mikkael A. Sekeres, MD, MS and Gail J Roboz, MD

1Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX; Houston, TX; 2Sarah Cannon Research Institute, Nashville, TN; 3H. Lee Moffitt Cancer Center, Tampa, FL; 4Oncology-Hematology Care, Cincinnati, OH; 5Cancer Care Center of South Texas, San Antonio, TX; 6Colorado Blood Cancer Institute, Denver, CO; 7Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD; 8Leukemia Program, Cleveland Clinic, Cleveland, OH; 9Joan and Sanford I. Weill Department of Medicine, Weill Cornell Medical College, New York, NY

Abstract #912: A Randomized, Placebo-Controlled, Phase II Study of Pracinostat in Combination with Azacitidine (AZA) in Patients with Previously Untreated Myelodysplastic Syndrome (MDS)

Pracinostat Placebo
CR, within 180 days 18% 33%
Best Response
Complete Remission 20% 33%
Partial Remission 0% 0%
Marrow CR 28% 22%
Stable Disease 26% 29%
Progressive Disease 6% 6%
Not evaluable 22% 10%

Aza + Pracinostat in MDS: Conclusions
- Pracinostat failed to improve the clinical effectiveness of Aza in this population of higher risk MDS
- Pracinostat resulted in more toxicity when added to Aza
  - Grade 3 Fatigue, 24% vs. 0%
  - Febrile Neutropenia, 33% vs. 18%
  - Thrombocytopenia, 47% vs. 26%
- This toxicity led to more, and earlier, drug discontinuation in the Pracinostat group
  - Drug discontinuations for adverse events, 26% vs. 10%
  - Not evaluable for response, 22% vs. 10%
- Exploratory analyses suggest that patients able to tolerate Pracinostat for at least 4 cycles may derive benefit
- Need consider alternative doses/schedules

Additional Analyses of a Randomized Phase II Study of Azacitidine Combined with Lenalidomide or with Vorinostat vs. Azacitidine Monotherapy in Higher-Risk Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML): North American Intergroup Study SWOG S1117 [Abstract 908]

Mikael A. Sekeres, MD, MS, Megan Othus, PhD, Alan F. List, MD, Olatoyosi Odunfa, MD, Richard M. Stone, MD., Steven D. Gore, MD, Mark R. Litzow, MD, Rena Buckstein, MD, Min Fang, MD, PhD, Diane Roulston, PhD, Clara D. Bloomfield, MD, Yanning Zhang, MD, Mario R. Velasco, MD, Rakesh Gaur, MD, MPH, Ehab Atallah, MD, Eyal C. Attar, MD, Frederick R. Appelbaum, MD, Harry P. Erba, MD

North American Intergroup Randomized Phase 2 MDS Study S1117: Study Design

Eligibility:
- Higher-risk MDS or CMML
- >18 years
- No previous allo HCT or exposure to any study drugs
- tMDS was allowed

Patients continued treatment until disease progression, relapse, “unacceptable” toxicity, or lack of response

Dose reductions allowed for unresolved grade ≥3 adverse events (per NCI CTCAE) or delayed count recovery

North American Intergroup Randomized Phase 2 MDS Study S1117: Grade ≥3 Toxicities

<table>
<thead>
<tr>
<th>Toxicity Variable</th>
<th>AZA</th>
<th>AZA+LEN (P-value vs. AZA)</th>
<th>AZA+VOR (P-value vs. AZA)</th>
<th>Total n=271</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia (n)</td>
<td>10</td>
<td>13 (.66)</td>
<td>12 (.51)</td>
<td>36</td>
</tr>
<tr>
<td>GI (n)</td>
<td>4</td>
<td>12 (.10)</td>
<td>14 (.02)</td>
<td>28</td>
</tr>
<tr>
<td>Rash (n)</td>
<td>3</td>
<td>14 (.01)</td>
<td>1 (.01)</td>
<td>17</td>
</tr>
<tr>
<td>Off tx due to toxicity/Side Effect/Complication</td>
<td>8%</td>
<td>20% (.05)</td>
<td>21% (.03)</td>
<td>18%</td>
</tr>
<tr>
<td>Non protocol defined dose modifications</td>
<td>24%</td>
<td>43% (.002)</td>
<td>42% (.01)</td>
<td>33%</td>
</tr>
</tbody>
</table>
North American Intergroup Randomized Phase 2 MDS Study S1117: Response

<table>
<thead>
<tr>
<th>Response Variable</th>
<th>AZA</th>
<th>AZA+LEN (P-value vs. AZA)</th>
<th>AZA+VOR (P-value vs. AZA)</th>
<th>Total n=277</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Tx Duration (Wks)</td>
<td>25</td>
<td>24</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Overall Response Rate (%)</td>
<td>38</td>
<td>49 (.16)</td>
<td>27 (.16)</td>
<td>38%</td>
</tr>
<tr>
<td>CR/PR/HR (%)</td>
<td>24/0/14</td>
<td>24/1/25</td>
<td>17/1/9</td>
<td>22/1/16%</td>
</tr>
<tr>
<td>CMML ORR (%)</td>
<td>5 (28)</td>
<td>13 (68) (.02)</td>
<td>2 (12) (.41)</td>
<td>37%</td>
</tr>
<tr>
<td>ORR Duration (median)</td>
<td>10 months</td>
<td>14 months (.41)</td>
<td>15 months (.31)</td>
<td>14 months</td>
</tr>
<tr>
<td>CMML ORR Duration (median)</td>
<td>15 months</td>
<td>14 months (.87)</td>
<td>24 months (.69)</td>
<td>15 months</td>
</tr>
</tbody>
</table>

North American Intergroup Randomized Phase 2 MDS Study S1117: Overall Survival All Patients

Sekeres et al. ASH 2015: 908a

MDS Summary

• We continue to explore and understand the biology of MDS
  – Role of somatic gene mutation.
  – Inflammation and MDS.
• The risk stratification models are further refined and will incorporate somatic gene mutation data in the near future.

MDS Summary

• In lower risk MDS promising results with
  – Lower dose HMA.
  – Eltrombopag for thrombocytopenia.
  – Luspatercept.
• Improving outcome in higher risk MDS remains an unmet need.

Sekeres et al. ASH 2015: 908a

North American Intergroup Randomized Phase 2 MDS Study S1117: Cautionsome [1]

No differences in ORR comparing AZA + LEN or AZA + VOR to AZA monotherapy.

Some subgroups (e.g., CMML) may have benefitted from AZA-based combinations.

Signal of OS improvement after failure -- ??Deeper Response ??

Sekeres et al. ASH 2015: 908a

Thanks!

Cleveland Clinic Leukemia/MDS Program

And Our Patients!!!