MDS: Update on Treatment and Side Effects Management

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Welcome and Introductions
Disclosures

Azra Raza, MD does not have any relevant financial relationships with any commercial interests to disclose.

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WHAT IS MDS?

Healthy Adult

Divide
Mature
Blood formation

RBC
WBC
Platelets

Divide
Mature

Anemia
Neutropenia
Thrombocytopenia

Divide
Do not mature

Trillion cells every 24 h.
IPSS for Risk Stratification

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score Value</th>
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</thead>
<tbody>
<tr>
<td>Bone marrow blasts</td>
<td>&lt; 5%</td>
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<tr>
<td></td>
<td>5% to 10%</td>
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<tr>
<td></td>
<td>11% to 20%</td>
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<tr>
<td></td>
<td>21% to 30%</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
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<td></td>
<td>--</td>
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<tr>
<td>Cytopenias†</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td>2/3</td>
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<td></td>
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Accurately predicts prognosis in ~39% patients

A Prognostic Nightmare

A case

• A 62-year-old man was discovered to have borderline cytopenias:
  – Hgb 11 g/dL
  – WBC 3.6
  – Platelet count 162,000
  – BM did not meet the minimal criteria for MDS (<10% dysplastic cells)
**ICUS**

**Idiopathic Cytopenia(s) of Undetermined (Uncertain) Significance (ICUS)**

1) Meaningful cytopenias
2) Does not meet minimal diagnostic criteria for MDS
   - > 10% dysplastic cells, or
   - 5%-19% blasts, or
   - Abnormal karyotype typical for MDS


**ICUS Natural History**

2,899 marrow exams for cytopenias at Mayo Clinic over 13 years

- 59%: MDS
- 18%: 535: non-MDS neoplasms
- 20%: 579: ?
- 2%: MDS-U

Hanson C and Steensma D. Abstract presented at: MDS Symposium; May 2009; Patras, Greece
Case Continued...

- Genetic profiling shows a mutation in TET2
- ICUS to CHIP

David P. Steensma et al. Blood 2015;126:9-16
Personalization: selection of homogenous groups

Morphologic Subtypes
Cytogenetics
Genetic Mutations
Response to Therapy

MDS Treatment Options
Curative

• Stem cell transplant

RIC Allo-transplant in MDS between 60-70 years

IPSS Low/Int-1

IPSS Int-2/High

RIC, reduced intensity conditioning.

Palliative

- ESA
- Lenalidomide
- Hypomethylating agents

Algorithm for treating lower risk MDS

Low and Int-1

- Sq-deletion ± other cytogenetic alterations?
  - Yes
  - Lenalidomide
  - No
  - Serum EPO ≤500 mU/mL?
    - Yes
    - EPO ± G-CSF Supportive care Clinical trial
    - No
    - Lenalidomide Azacitidine Decitabine ATG ± cyclosporine Supportive care Clinical trial
Epo Improves Anemia in a Subset of Patients With MDS

- According to a meta-analysis, mean response rates range from 15% to 20%\textsuperscript{1}
- Predictors for good response include serum Epo level and transfusion need\textsuperscript{1}
  - <500 U/L and limited prior need for transfusion\textsuperscript{1}
- Most responses to ESA occur within 8 weeks of treatment, some patients respond after 12 weeks\textsuperscript{2,3}

ESA, erythropoiesis-stimulating agent.


LENALIDOMIDE

Transfusion-dependent anemia due to low- or Int-1–risk MDS associated with del(5q) with or without additional abnormalities

With del(5q)\textsuperscript{1}

Without del(5q)\textsuperscript{2}

Responders

Nonresponders

Lenalidomide Toxicity

- Allergic reactions
  - Scalp itching
  - Rash
  - Controlled mostly by Benadryl® (diphenhydramine), occasional steroid use
- Diarrhea
  - Lomotil® (diphenoxylate and atropine)
- Myelosuppression

References:

Most Frequently Observed Hematological Adverse Events: del 5q MDS Safety Data

<table>
<thead>
<tr>
<th></th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>58.8%</td>
<td>53.4%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>61.5%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Anemia NOS</td>
<td>11.5%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Leukopenia NOS</td>
<td>8.1%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

- Grade 3/4 febrile neutropenia was reported in 4.1% (6/148) of MDS patients
- In registration trial, G-CSFs were permitted for patients who developed neutropenia or fever in association with neutropenia
- Patients may require the use of blood product support and/or growth factors
Dose Modification

• Reserved for patients experiencing a 50% or greater decline in ANC or platelet count

• Treatment with Lenalidomide should be held until toxicity resolves and then resumed as follows
  – 5mg/day for patients at 10mg/day
  – 5 mg/every other day
  – 5 mg twice weekly dose as long as there are no signs of disease progression


HMAs in Lower Risk MDS

• Limited data
  – In transfusion-dependent, lower-risk MDS resistant to ESA, HMA therapy results in approximately 17% transfusion independence

Algorithm for treating higher risk MDS

Is a donor available for bone marrow transplantation?

Yes → Is the patient fit for transplantation?

Yes → Bone marrow transplantation

No → Hypomethylating agents

No → Response

High/Int-2 patient

Is a donor available for bone marrow transplantation?

Yes

No

Yes

No

Experimental Drugs

Adapted from NCCN Guidelines on Myelodysplastic Syndromes V.1.2009.

Azacitidine (VIDAZA®) Efficacy: CALGB 9221

• Clinical Benefit
  • 40% of patients treated with VIDAZA experienced clinical benefit
    • 16% responded (CR + PR) and 24% improved

*Per the Study 9221 response criteria.
†Patients who had positive changes in peripheral counts but did not meet criteria for CR or PR were considered improved.

VIDAZA full prescribing information.
VIDAZA®:
Most Commonly Occurring Adverse Reactions
(All Grades) in CALGB Studies 9221 and 8921 (SC Route)

<table>
<thead>
<tr>
<th>Preferred Term (CALGB Criteria)</th>
<th>Observation n = 92 (%)</th>
<th>All VIDAZA (SC) n = 220 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>16 (17.4)</td>
<td>155 (70.5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>59 (64.1)</td>
<td>153 (69.5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>42 (45.7)</td>
<td>144 (65.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (5.4)</td>
<td>119 (54.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>28 (30.4)</td>
<td>114 (51.8)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>27 (29.3)</td>
<td>106 (48.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (14.1)</td>
<td>80 (36.4)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>0</td>
<td>77 (35.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (6.5)</td>
<td>74 (33.6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10 (10.9)</td>
<td>71 (32.3)</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>14 (15.2)</td>
<td>67 (30.5)</td>
</tr>
</tbody>
</table>

VIDAZA full prescribing information.

Study 9221: Maximizing Response With VIDAZA®

- Achievement of PR was initially reported between the 2nd and 19th treatment cycles*
- Achievement of CR was between the 8th and 15th treatment cycles†
- Continue therapy beyond the initial benefit to achieve full benefit for patients

*The median number of cycles needed to achieve a PR was 7
†The median number of cycles needed to achieve a CR was 8

Celgene Corporation, Data on File.
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 Giagounidisis, 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

Overall Survival: Azacitidine vs CCR
ITT Population

Log-Rank p=0.0001
Difference: 9.4 months

Proportion Surviving

Time (months) from Randomization
Meaningful responses to both drugs generally short-lived in small subsets of patients
Genomics in Cancer Care

What is genomics? Genomics is the study of the entire genome.

“PANOMICS”
Will this cure MDS?

Convert MDS into a chronic disease that patients can live with and not die from

More Than One Way to Build Bridges!
Proud to partner in the MOONSHOT 2020
Managing Treatment Side Effects of MDS

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MDS Center
Columbia University Medical Center
Herbert Irving Pavilion
New York, NY

Common Side Effects of Treatments

A. Erythropoietin Stimulating Agents (ESA):
• Procrit® (epoetin alfa) or Aranesp® (darbepoetin alfa)
  – SQ (weekly or bi-weekly)
  Hgb < 10 gms
• S/E:
  – Headaches
  – Body aches
• Management:
  – Acetaminophen
B. Lenalidomide – 10 mg po daily x 28 days every month

- S/E:
  - Myelosuppression
  - Allergic reactions - rash/scalp itching
  - Diarrhea

- Management:
  - Weekly blood counts
  - Dose modifications
  - Growth factors
  - Transfusions
  - Antibiotics
  - Anti-histamine/Steroids
  - Anti-diarrhea

C. Hypomethylating Agents:
Azacitidine and Decitabine – IV or SQ for 5 or 7 days every 4 weeks

- S/E:
  - Nausea
  - Cytopenias
  - Constipation
  - Infection

- Management:
  - Antiemetics (e.g. Kytril®/Zofran®)
  - Transfusions
  - Growth factors
  - Stool softener/laxatives (e.g. Colace®/Miralax®)
  - Antibiotics
  - Dose modifications – dose delay and dose reduction
D. Iron Chelating Agents:
Deferasirox (Exjade® or Jadenu®) – oral once daily

• S/E:
  – Abdominal pain
  – Diarrhea
  – Nausea and vomiting
  – Rash

• Management:
  – Antidiarrheals (e.g. Imodium®, Lomotil)
  – Antiemetics (e.g. Kytril, Zofran)
  – Antihistamines (e.g. Benadryl)
  – Steroids – Topical or Medrol® dose pack
  – Dose modifications

Patient Assistance:
www.oncologyaccessnow.com/index.jsp - Novartis
www.revlimid.com/mm-patient/affording-revlimid/financial-assistance - Celgene
www.panfoundation.org - Patient Access Network Foundation
www.LLS.org/copay - The Leukemia & Lymphoma Society

MDS Resources:
www.LLS.org/MDS
www.LLS.org/educationvideos
www.mdsbeacon.com/links/support-groups
www.mds-foundation.org/global-patient-support-groups
www.mdscenterfornurses.com/nurse-and-patient-resources
www.aamds.org
References:

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Question & Answer Session
The speakers' slides are available for download at www.LLS.org/CE
The Leukemia & Lymphoma Society (LLS) offers:

- Live, Online Chats provide a friendly forum for patients to share experiences: www.LLS.org/chat

- What to ask: Lists of suggested questions for patients to ask the healthcare team. Share question guides with your patients: www.LLS.org/whatatoask

- LLS Online Social Network for HCPs and patients to seek answers and share information: www.CommunityView.LLS.org

Information Resource Center:
Speak one-on-one with an Information Specialist who can assist patients and healthcare professionals through cancer treatment, including clinical trial searches, financial and social challenges.

- EMAIL: infocenter@LLS.org
- TOLL-FREE PHONE: (800) 955-4572

MDS: Update on Treatment and Side Effects Management

The Leukemia & Lymphoma Society (LLS) offers:

Free education materials: www.LLS.org/publications

Continuing education programs and videos: www.LLS.org/professionaled