What do patients recall being told about MDS?

- Survey of 358 patients via AA&MDSIF

### Table 1. Baseline demographics and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 358</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age, yrs</td>
<td>65 (19–91)</td>
</tr>
<tr>
<td>Male, %</td>
<td>49</td>
</tr>
<tr>
<td>Median (range) time since diagnosis, yrs</td>
<td>3 (0–29)</td>
</tr>
<tr>
<td>Median (range) time since first detection of abnormal blood profile, yrs</td>
<td>6 (0–59)</td>
</tr>
<tr>
<td>IPSS risk category, %</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>28</td>
</tr>
<tr>
<td>Int-1</td>
<td>39</td>
</tr>
<tr>
<td>Int-2</td>
<td>23</td>
</tr>
<tr>
<td>High</td>
<td>9</td>
</tr>
<tr>
<td>Bone marrow not known, %</td>
<td>42</td>
</tr>
<tr>
<td>Cytogenetic status not known, %</td>
<td>28</td>
</tr>
<tr>
<td>Cytopenias, %</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>82</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>45</td>
</tr>
<tr>
<td>Blood transfusions, %</td>
<td>65</td>
</tr>
<tr>
<td>Within 3 mos</td>
<td>52</td>
</tr>
<tr>
<td>Treatments in the last 3 mos before survey, %</td>
<td></td>
</tr>
<tr>
<td>Darbepoetin</td>
<td>55</td>
</tr>
<tr>
<td>Epoetin</td>
<td>49</td>
</tr>
<tr>
<td>Active therapies</td>
<td></td>
</tr>
<tr>
<td>Azacitidine</td>
<td>51</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>39</td>
</tr>
<tr>
<td>Decitabine</td>
<td>56</td>
</tr>
<tr>
<td>Antithymocyte globulin</td>
<td>11</td>
</tr>
<tr>
<td>Stem cell or bone marrow transplantation</td>
<td>10</td>
</tr>
<tr>
<td>Enrollment in a clinical trial</td>
<td>24</td>
</tr>
</tbody>
</table>

*aOnly 45% of all patients knew their IPSS score.

Abbreviations: Int, Intermediate; IPSS, International Prognostic Scoring System.
Demographics of Germany [1910 – 2050] and Europe

Eurostat 2004-Percentage of people over age of 60 years in 2031
The Bone Marrow Failure Syndromes

AA – Aplastic Anaemia
PNH – Paroxysmal Nocturnal Haemaglobinuria

MDS

Low Risk

5q-

High Risk

AML

Adapted from N. Young
What do patients recall being told about MDS?

- Survey of 358 patients via AA&MDSIF:
  - How was MDS first described to you?

Sekeres M et al Oncologist 2011; Epub Apr 8.
Low Risk MDS

- 5-9% blasts
- 10-19% blasts
- AML >20% blasts

2008 World Health Organization (WHO) Classification of Chronic Myeloid Neoplasms

Requirements: <20% bone marrow blasts
No AML-defining chromosomal abnormality

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

- Chronic myelomonocytic leukemia (CMML)

MDS/MPN, unclassifiable

Myelodysplastic syndromes (MDS)

- Refractory cytopenia with unilineage dysplasia
  - 3 categories:
    - Refractory anemia (RA)
    - Refractory neutropenia (RN)
    - Refractory thrombocytopenia (RT)

- Refractory anemia with ring sideroblasts (RARS)
- Refractory cytopenias with multilineage dysplasia (RCMD)
- Refractory anemia with excess blasts - 1 (RAEB-1)
- Refractory anemia with excess blasts - 2 (RAEB-2)
- MDS with isolated del(5q)
- MDS, unclassifiable

Steensma 2008
MDS Classification – The *Ultimate* Simplification

• **Lower Risk**  *(Survival 3-10 years, low rate of AML)*
  – RA, RARS
  – RCUD, RCMD
  – MDS-U, MDS del (5q)
  – IPSS Low, Int-1 (Score 0-1.0)

• **Higher Risk**  *(Survival <1.5 years, high rate of AML)*
  – RAEB (-1, -2)
  – IPSS Int-2, High (Score ≥ 1.5)
# International Prognostic Scoring System version 1.0 (1997)

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Marrow blasts (%)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Karyotype class*</td>
<td>Good</td>
</tr>
<tr>
<td># of cytopenias**</td>
<td>0 or 1</td>
</tr>
</tbody>
</table>

*Karyotypes:* Good = normal, -Y, del(5q) alone, del(20q) alone; Poor = chromosome 7 abnormalities or complex; Intermediate = other karyotypes

**Cytopenias:** Hb < 10 g/dL, ANC <1800/uL, platelets <100,000/uL

## IPSS Risk Categories: Patient Distribution And Outcomes

<table>
<thead>
<tr>
<th>Score sum</th>
<th>IPSS Risk Category</th>
<th>Median survival for over age 60 group (years)</th>
<th>Time until 25% get AML (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>Int-1</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>Int-2</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>&gt;=2.5</td>
<td>High</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

CMML (chronic myelomonocytic leukaemia)

• Not CML!!

<table>
<thead>
<tr>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
</tr>
<tr>
<td>WBC &gt; 15 × 10^9/L</td>
</tr>
<tr>
<td>Anemia, yes*</td>
</tr>
<tr>
<td>Platelets &lt; 100 × 10^9/L</td>
</tr>
<tr>
<td>ASXL1 mutated, yes</td>
</tr>
</tbody>
</table>
Therapeutic goals

Low risk MDS infection, bleeding anaemia

Ineffective haematopoiesis

High risk MDS delay/stop progression

AML evolution

Quality of life

survival

MDS
This is a Hard Truth

The only therapy capable of curing MDS is a bone marrow transplantation.

All other therapies improve blood counts, minimize transfusions, or improve quality of life.

If your blood counts and quality of life are fine, and you don’t need transfusions, you may not need therapy.
Medications Currently Commonly Used for Patients with MDS

**FDA Approved for MDS-Related Indications**

- Hypomethylating agents / DNA methyltransferase inhibitors / epigenetic drugs
  - Azacitidine (Vidaza ®) Approved May 2004
  - Decitabine (Dacogen ®) Approved May 2006
  - Immunomodulatory drug (iMiD)
    - Lenalidomide (Revlimid ®) Approved December 2005
  - Iron chelators
    - Deferasirox (Exjade ®) Approved November 2005
    - Deferoxamine (Desferal ®) Approved 1968

**FDA Approved for Other Indications**

- Blood cell (hematopoietic) growth factors
  - Red cell growth factors
    - Epoetin alfa (Procrit ®)
    - Darbepoetin alfa (Aranesp ®)
  - White cell growth factors
    - Filgrastim, G-CSF (Neupogen ®)
    - Pegfilgrastim (Neulasta ®)
  - Platelet growth factors
    - Romiplostim (NPlate ®)
  - Eltrombopag (Promacta ®)
- Immunosuppressive drugs
  - Thalidomide, androgens, other biologics
- Chemotherapy or stem cell transplant
# Supportive care

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red cell transfusion</strong></td>
<td>Anaemia causing symptoms</td>
</tr>
<tr>
<td><strong>Platelet transfusion</strong></td>
<td>Low platelets-bleeding &amp; bruising</td>
</tr>
<tr>
<td></td>
<td>Planned surgical operation</td>
</tr>
<tr>
<td><strong>Erythropoietin</strong></td>
<td>Anaemia</td>
</tr>
<tr>
<td><strong>Granulocyte-colony stimulating factor</strong></td>
<td>Infections associated with low white count</td>
</tr>
<tr>
<td><strong>Antibiotic</strong></td>
<td>Infections</td>
</tr>
<tr>
<td><strong>Iron chelation therapy</strong></td>
<td>Patients with low-risk disease with high transfusion requirement</td>
</tr>
</tbody>
</table>
## Incidence of RBC Transfusion Dependence in MDS

<table>
<thead>
<tr>
<th>IPSS Category</th>
<th>Proportion RBC Transfusion Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>39%</td>
</tr>
<tr>
<td>Intermediate-1 Risk</td>
<td>50%</td>
</tr>
<tr>
<td>Intermediate-2 Risk</td>
<td>63%</td>
</tr>
<tr>
<td>High Risk</td>
<td>79%</td>
</tr>
</tbody>
</table>

Brechignac S et al *Blood* 2004 104;236b (abstract 4716)
Red Cell Transfusion... The good

- Improves the oxygen carrying ability and improves symptoms

- Many patients will develop symptoms due to anaemia

- Red cell transfusion is the commonest way anaemia is treated

- The number and frequency may vary, but generally needs increase over time

- Sense of Altruism for donors—all voluntary
............ The bad

- Costly and decreasing donor pool
- Impacts on QOL, hospital attendances
- Transfusion reaction, infections and alloimmunisation
- Each unit has 250 mg of elemental iron
Chelation Clinical Guidelines

- Many organizations have guidelines for iron monitoring and iron chelation in MDS
  - At least 8 different guidelines in the last 10 years
  - Only partially evidence-based
- In general, these guidelines suggest:
  - **Periodic serum ferritin monitoring**, supplemented by other techniques for assessing iron burden
  - Consideration of iron chelation when patient has **persistent ferritin >1000 ng/mL** or other evidence of iron overload such as MRI, and lower-risk MDS
  - Start thinking about iron overload after **20-50 units RBCs**
And now **Iron** in MDS?...

**Therefore**...

- **Iron**
- **End Organ Damage**
- **Chelation**
- **Iron**
- **End Organ Damage**
Platelet transfusion-Liquid Gold

- Platelet transfusion should be reserved for patients with bruising or bleeding symptoms
- Planned surgery, dental extraction may also need to be covered by platelet transfusion
Therapy in low risk MDS

• Squeeze every ounce of production out of the remaining functional bone marrow cells by ERYTHROPOIETIN (EPO) and GROWTH FACTORS (eg GCSF) injections
ESAs/GF in MDS: Who Responds?

RA, RARS, RAEB

Score > +1
Good response
74%, n=34

Score -1 to +1
Intermediate response
23%, n=31

Score < -1
Poor response
7%, n=29

Treatment response score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>s-epo</td>
<td>&lt;100</td>
<td>+2</td>
</tr>
<tr>
<td>U/L</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>

Therapy in low risk MDS

• Blocks the effects of nasty cytokines (chemicals produced in excess by abnormal bone marrow cells which can kill the normal cells)

eg. Lenalidomide

ATG (horse or rabbit)
High risk MDS

• Replace the bone marrow (and immune system)
  Bone marrow transplant
  Chemotherapy
  Azacitidine/Decitabine
  Clinical trials/ novel agents
Goal of Therapy: Higher-risk MDS

Prevent methyl groups from inactivating tumor suppressor genes and be directly cytotoxic – kill those bad cells!

• Azacitidine (Vidaza)
• Decitabine (Dacogen)
Azacitidine in high-risk MDS

It has been suggested that azacitidine may switch on important anti-cancer genes

- Reduced red cell transfusion
- Improvement in survival
- Less chance of MDS deteriorating
- Results not influenced by patient age, blast cells, karyotype

Administered as injection into skin
For high risk patients ineligible for transplantation
Overall Survival: Azacitididine 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

Treatment algorithm for patients with MDS*

Low risk

Asymptomatic
- Observation
- EPO/G-CSF
- Azacitidine
- Decitabine
- Lenalidomide
- Thalidomide
- Investigational

Symptomatic
- Transfusion
- SCT ablative
- RIC

High risk

Survival

Blasts

Asymptomatic
- BM function

Symptomatic
- Lenalidomide
- Azacitidine
- Thalidomide
- Decitabine
- Investigational

5q-

Complex

7q

Azacitidine
- Decitabine
- Investigational
- Intensive chemotherapy

RIC
SCT – full ablative

Myelodysplasia
INTENSIVE TREATMENT

Bone marrow transplant should be considered when ‘curative’ therapy is thought to be appropriate.

Key issues for patients:

Motivated, and deemed fit for BMT

‘High-risk’ MDS, with disease under control

Appropriate counselling regarding outcomes, risks, and intensive long-term follow-up
Newer developments

• Genes, genes and more genes
• New risk scoring system-IPSS-R
• Oral azacitidine
• Newer targeted therapy/personalised medicine
• Lenalidomide approved for 5q- syndrome (cancer drug fund and also NICE approved)
• CMML- what is it??
Gene Mutations in MDS

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

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

Transcription Factors
- RUNX1
- ETV6
- GATA2
- EP300
- WT1
- PHF6

Splicing Factors
- SF3B1
- U2AF1
- SRSF2
- SF1
- ZRSF2
- U2AF2
- PRPF40B
- PRPF8
- U2AF1

Others
- TP53
- NPM1
- BCOR
- RNA helicases
- GNAS/GNB1
- NPM1
- Cohesins
- RTK's
- SF1

Others
- BCOR
- RNA helicases
- GNAS/GNB1
- NPM1
- Cohesins
- RTK's
- SF1

Agents in clinical development for AML/MDS

**Agents Directly Targeting Tumors**

*In AML with Intermediate or Unfavorable cytogenetics

^In untreated AML ineligible for intensive chemotherapy

^^Bortezomib + Sorafenib

$ Also in patients ineligible for standard chemotherapy

<table>
<thead>
<tr>
<th>Line Of Therapy</th>
<th>Biomarker Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Line Defined</td>
<td>No Biomarker</td>
</tr>
<tr>
<td>Induction/Consolidation</td>
<td>Conditioning</td>
</tr>
<tr>
<td>Transplant Related</td>
<td>SC Stem Cells</td>
</tr>
<tr>
<td>Conditioning</td>
<td>Maintenance</td>
</tr>
</tbody>
</table>

**Mechanism of Action**

1. Aurora kinase inhibitor
2. JAK 3 Beta inhibitor
3. FGFR inhibitors
4. CD33 linked immunoconjugate
5. HDAC inhibitors
6. CDK 5 antagonist
7. Proteasome inhibitor
8. Lipo peptide inhibitor
9. RNA inhibitors
10. IGF1 protein inhibitor

11. Lysyl dehydrogenase stimulant
12. IGF1 receptor inhibitor
13. Ubilin polymerization inhibitors
14. Sphosine-rich oligonucleotide aptamer
15. Hexose and AKT1C3 activated alkylator
16. Akt-inhibitor
17. Bcr-abl tyrosine kinase inhibitor
18. BIRC5 protein inhibitor
19. CXCR4 receptor antagonist
20. Dual Src kinase and pre-tubulin inhibitor
21. Dual TKI-FLT3 and KIT inhibitor
22. EGFR inhibitor
23. FLT-3 inhibitor
24. JAK inhibitors
25. MEK inhibitor
26. mTOR inhibitor
27. Multi TKI
28. PDCD 1 protein inhibitor
29. PDGFR inhibitor
30. PI3K inhibitor
31. Immunomodulators
32. Supportive Care

Source: 1. ADIS Insight; 2. TrialTrove; 3. Company Website
Conclusion

• MDS is more common than we think!
• Delay therapy until symptoms develop or needing transfusions
• Treatment based on the risk of disease- low risk versus high risk
• Optimistic future-novel drugs in early phase clinical trials
• Personalised gene sequencing and individualised therapy-THE FUTURE !!
100 Questions & Answers

About

Myelodysplastic Syndromes

by

Jason Gotlib, MD, MS
Lenn Fechter, RN, BSN

Prof Ghulam Mufti

Staff and patients at
Kings College Hospital

LEUKAEMIA & LYMPHOMA RESEARCH
Beating Blood Cancers