Myelodysplastic Syndromes

Austin Kulasekararaj
Scheme

• Terminology and History
• Incidence
• Blood cell production
• Symptoms
• Diagnostic tests
• Therapeutic options
• Survey of patients
• Conclusion
MDS-Definition

- A heterogenous clonal disorder derived from an abnormal multipotent progenitor cell.

- It is characterised by hyperproliferative bone marrow, dysplasia, ineffective haematopoiesis leading to cytopenias.
What does the term "myelodysplastic" actually mean?

• **Myelo** = marrow
• **Dysplastic** = abnormal or just gone bad or funny looking

Bone marrow cells fail to make enough healthy blood cells—quantity and quality is affected.

• Crowding out remaining normal cells (Cancer)
Bone Marrow Basics

Stem Cells

Bone Marrow

Blood Stream

Red Blood Cells
20 trillion

White Blood Cells
Platelets
MDS in the Bone Marrow (II)

Stem Cells

Bone Marrow

Red Blood Cells

White Blood Cells

Platelets
MDS features

All people with MDS have two things in common

- Low count for at least 1 blood cell type (cytopenia)
- Bone marrow and blood contain blood cells with an abnormal shape, size, or look.
Symptoms of MDS

Asymptomatic – abnormal blood count

Fatigue, lack of energy and shortness of breath
  - caused by anaemia (low red cells)

Bruising and bleeding
  - caused by low platelet cell count

Infection
  - due to low numbers and/or poorly functioning white cells
Patients

Median age is @ 72 years

Prior exposure to chemo and or radiotherapy, but 90% do not have any known exposures

Clinical Course

MDS

25% → AML

50% → Infection, Bleeding and treatment complications

25% → Unrelated causes
Bone marrow aspirate and trephine

Diagnostic Tests

Blood film/Aspirate  Trephine  Cytogenetics  Flow Cytometry
Morphology of MDS

Blasts (Type 1 and 2)

RARS
Demographics of Germany [1910 – 2050] and Europe

Country by rank order in 2031

Percentage

2031

2004

Statistisches Bundesamt, 2002

Eurostat 2004-Percentage of people over age of 60 years in 2031
Hematologic Malignancy

Myeloid Cancer

Chronic Myeloid Disorders

Acute Myeloid Leukemia

≥20% marrow "blasts"

Lymphoid Cancer

Lymphoma (Hodgkin, NHL)

Plasma Cell Disorders (Myeloma)

Acute Lymphoid Leukemia

MDS is in here – in the "shadowlands" between cancer and not cancer
The Bone Marrow Failure Syndromes

AA – Aplastic Anaemia
PNH – Paroxysmal Nocturnal Haemoglobinuria

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?
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

Low Risk MDS

- 5-9% blasts
- 10-19% blasts
- AML >20% blasts
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>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow blasts (%)</td>
<td>&lt;5%</td>
<td>5-10%</td>
<td>--</td>
<td>11-20%</td>
<td>21-30%</td>
</tr>
<tr>
<td>Karyotype class*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td># of cytopenias**</td>
<td>0 or 1</td>
<td>2 or 3</td>
<td>--</td>
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<td>--</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>

#### Patient Distribution
- Low Risk, 31%
- Int-1 Risk, 39%
- Int-2 Risk, 22%
- High Risk, 8%

Therapeutic Options

- **Low Risk MDS** –
  - Main problem is anaemia, bleeding and recurrent infections

- **High Risk MDS** –
  - Main problem is bone marrow failure and risk of leukaemia
Treatment: general concepts

Treatment choices should take into account:

<table>
<thead>
<tr>
<th>What type of MDS does the patient have?</th>
<th>How aggressive is their MDS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are any symptoms particularly bothersome?</td>
<td>How does the patient want to be treated?</td>
</tr>
<tr>
<td>Is curative therapy appropriate?</td>
<td>What age?</td>
</tr>
<tr>
<td></td>
<td>What other problems?</td>
</tr>
</tbody>
</table>
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
  - Epoetin alfa (Procrit®)
  - Darbepoetin alfa (Aranesp®)
- Red cell growth factors
  - Filgrastim, G-CSF (Neupogen®)
  - Pegfilgrastim (Neulasta®)
- White cell growth factors
  - Platelet growth factors
  - Immunosuppressive drugs
  - Thalidomide, androgens, other biologics
  - Chemotherapy or stem cell transplant
<table>
<thead>
<tr>
<th>Supportive care</th>
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<tbody>
<tr>
<td><strong>Red cell transfusion</strong></td>
</tr>
</tbody>
</table>
| **Platelet transfusion** | Low platelets-bleeding & bruising  
Planned surgical operation |
| **Erythropoietin** | Anaemia |
| **Granulocyte-colony stimulating factor** | Infections associated with low white count |
| **Antibiotic** | Infections |
| **Iron chelation therapy** | Patients with low-risk disease with high transfusion requirement |
## 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
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**
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>Change</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>s-epo</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
  - Azacitidinе/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

Benefits include:
- 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 (oral azacitidine!)

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

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
Treatment algorithm for patients with MDS*

Low risk

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

Symptomatic
- Transfusion
- Lenalidomide
- EPO/G-CSF
- Azacitidine
- Thalidomide
- Decitabine
- Investigational

High risk

5q-

7q

Complex

Observation

Azacitidine
Decitabine
Investigational

Intensive chemotherapy
RIC

SCT – full ablative

SCT ablative
RIC

What do patients recall being told about MDS?

- Survey of 358 patients via AA&MDSIF

<table>
<thead>
<tr>
<th>Table 1. Baseline demographics and disease characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Median (range) age, yrs</td>
</tr>
<tr>
<td>Male, %</td>
</tr>
<tr>
<td>Median (range) time since diagnosis, yrs</td>
</tr>
<tr>
<td>Median (range) time since first detection of abnormal blood profile, yrs</td>
</tr>
<tr>
<td>IPSS risk category, %</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Int-1</td>
</tr>
<tr>
<td>Int-2</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Bone marrow not known, %</td>
</tr>
<tr>
<td>Cytogenetic status not known, %</td>
</tr>
<tr>
<td>Cytopenias, %</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Blood transfusions, %</td>
</tr>
<tr>
<td>Within 3 mos</td>
</tr>
<tr>
<td>Treatments in the last 3 mos before survey, %</td>
</tr>
<tr>
<td>Darbepoetin</td>
</tr>
<tr>
<td>Epoetin</td>
</tr>
<tr>
<td>Active therapies</td>
</tr>
<tr>
<td>Azacitidine</td>
</tr>
<tr>
<td>Lenalidomide</td>
</tr>
<tr>
<td>Decitabine</td>
</tr>
<tr>
<td>Antithymocyte globulin</td>
</tr>
<tr>
<td>Stem cell or bone marrow transplantation</td>
</tr>
<tr>
<td>Enrollment in a clinical trial</td>
</tr>
</tbody>
</table>

*aOnly 45% of all patients knew their IPSS score. Abbreviations: Int, Intermediate; IPSS, International Prognostic Scoring System.

Abnormal blood test

3 years

Diagnosis of MDS
Table 2. Patient-reported number of days when health was “not good” or restricted activities in the last 30 days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall</th>
<th>By treatment</th>
<th>By IPSS risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Active treatment</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Not good physical health, days</td>
<td>8.3</td>
<td>8.8</td>
<td>8.1</td>
</tr>
<tr>
<td>Not good mental health, days</td>
<td>6.8</td>
<td>7.0</td>
<td>6.7</td>
</tr>
<tr>
<td>Physical or mental health restricting usual activities, days</td>
<td>6.8</td>
<td>7.9</td>
<td>6.4</td>
</tr>
</tbody>
</table>

*aThere were no significant differences between active treatment and supportive care for each parameter investigated. Abbreviation: IPSS, International Prognostic Scoring System.*
Conclusions

- MDS is more common than you think!
- Most people with MDS have some anemia
- We can delay therapy until symptoms or transfusions demand it
- Therapy choices depend on whether you have lower- or higher-risk MDS – so make sure you ask your doctor your MDS subtype & IPSS Score!