MDS - Diagnosis and Treatments

Dr Helen Enright, Adelaide and Meath Hospital
Dr Catherine Flynn, St James Hospital
Overview

What is myelodysplasia?

Symptoms

Diagnosis and prognosis

Myelodysplasia therapy
  Supportive care
  Non-intensive therapy
  Bone marrow transplant
Age-related Incidence of MDS

Age in 5-year blocks

(Per 100,000)

What causes MDS?

- Damage to marrow cells
  - Previous chemotherapy
  - Previous radiation therapy
  - Exposure to marrow-damaging agents (??)
  - Predisposition?????
What is Myelodysplasia?

Myelodysplastic syndromes are a group of blood stem cell disorders of varying severity typified by:

- Low blood counts (marrow failure)
- Typical marrow features
- Possibility of progressing to leukaemia (in some patients)
What is Myelodysplasia?

Normal bone marrow makes healthy blood cells (red, white and platelet cells)

In MDS, the bone marrow makes the blood cells badly (dysplasia), causing low blood counts and cells that don’t work very well
Myelodysplasia Symptoms

None – abnormal blood count

Fatigue 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
Diagnosis

Specialist tests for myelodysplasia

- Bone marrow sample
- Morphology
- Flow cytometry
- Cytogenetics
## Diagnosis

### WHO Classification of myelodysplasia

<table>
<thead>
<tr>
<th>Entity</th>
<th>Bone marrow blasts</th>
<th>Cytogenetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>5q- syndrome</td>
<td>&lt;5%</td>
<td>5q- only</td>
</tr>
<tr>
<td>Refractory anaemia</td>
<td>&lt;5%</td>
<td>various</td>
</tr>
<tr>
<td>Refractory cytopenia multilineage dysplasia (RCMD)</td>
<td>&lt;5%</td>
<td>various</td>
</tr>
<tr>
<td>Refractory anaemia excess blasts-1 (RAEB-1)</td>
<td>5-9%</td>
<td>various</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>10-19%</td>
<td>various</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukaemia -1 (CMML-1)</td>
<td>&lt;10%</td>
<td>various</td>
</tr>
<tr>
<td>CMML-2</td>
<td>10-19%</td>
<td>various</td>
</tr>
</tbody>
</table>
International Prognostic Scoring System

Low

INT-1

INT-2

HIGH

Severity
Therapeutic Options

- Low Risk MDS –
  - Main problem is anaemia, sometimes thrombocytopenia

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

general concepts

Treatment choices should take into account:

- What type of MDS does the patient have?
- How aggressive is their MDS?
- Are any symptoms particularly bothersome?
- How does the patient want to be treated?
- Is curative therapy appropriate?
- What age?
- What other problems?
What is supportive care?

Supportive care is any medicine or device that helps to make symptoms go away, or makes it easier and safer for the patient to receive ‘active’ treatment.....
## Supportive care

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

Symptomatic anaemia in low risk MDS

- Transfusion
- Growth Factors
- Immunosuppression with Antithymocyte globulin
- Lenalidomide in 5q-
Myelodysplasia supportive care

Supportive care

Red cell transfusion

- 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
Myelodysplasia supportive care

Supportive care

Platelet transfusion

- 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
Myelodysplasia supportive care

Erythropoietin

- May improve anaemia in patients with MDS
- May reduce red cell transfusion need
- Seems to work best when given with white cell growth factor G-CSF
- Has to be given by injection
20 Years experience of erythropoietin +/- G-CSF therapy in MDS

- Overall response rate ~20-40%
- Best response group ~ 60-70%

(Low erythropoietin blood levels, not needing much transfusion)
Questions regarding Erythropoietin in MDS

- Is there a quality of life benefit for EPO responders?
- Is EPO therapy cost-effective?
- Is there a survival advantage for EPO responders?
Myelodysplasia supportive care

**Iron overload**
- Long term red cell transfusion can lead to increased iron that the body can’t get rid of
- Increased iron may damage organs like the heart, liver, and pancreas

**Iron chelation (removal)**
- Considered in transfusion dependent MDS patients with low risk MDS with a high transfusion requirement
- Desferrioxamine (injection) and Deferiprone (tablet) are used to remove iron
Which patients if any should get iron chelation?

- IPSS score low or int-1
- Ferritin should be 1000-2000 ng/ml or clinical or radiological evidence of iron loading
- This would often correlate with 20-30 units of red cells transfused
- Some candidates for transplant in whom there is a significant delay until the procedure
We have still not answered two major questions in low risk MDS!

- Is erythropoietin therapy more beneficial than transfusion?
- Is iron chelation therapy beneficial?:
Clinical Trials may answer some of these questions

- Erythropoietin versus Placebo
- Iron chelation versus Placebo
Best supportive care

- Red cell transfusion as required – to maintain quality of life
- Antibiotics for treatment and prevention of infections
- G-CSF during infection (if white cell count low)
- Iron chelation therapy if needed
MDS Treatment Options

Can we move beyond supportive care to

- Change the course of MDS?
- Delay progression?
- Delay/prevent leukaemia development
- Cure????
Therapeutic Options

- **Low Risk MDS**
  - Supportive care/ blood transfusion /iron Chelation
  - Erythropoietic stimulating agent (ESA)
  - Immunosuppression
  - Lenalidomide

- **High Risk MDS**
  - Supportive care
  - Azacitidine
  - Chemotherapy
  - Stem cell transplantation
Myelodysplasia
Non-intensive therapy

5q- Syndrome MDS
5% of MDS patients have 5q-MDS

- Usually female
- ‘Good’ platelet count
- Anaemia
- Chromosome 5q missing
- Good prognosis

Lenalidomide
Should be considered for 5q- syndrome

- Oral medication
- Eliminates need for transfusion in 67% of patients
5q- Syndrome

del(5)(q31q33)
Transfusion Independence Response
Lenalidomide in 5q- syndrome

N = 148

Transfusion Independence

99 (67%)

Average time to response, weeks (range)

4.6 (1 - 49)
Azacitidine in high-risk MDS

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

Significant benefit to patients with aggressive MDS when treated with Azacitidine in clinical trials (USA and Europe)

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

- Drug administered by injection (oral preparation in development)
- Well tolerated
- May be appropriate for high risk MDS patients who are not candidates for transplantation
Intensive Chemotherapy for MDS

- Sometimes used in high-risk MDS
- Can reduce leukemia cells in patients who are progressing
- Sometimes used in patients prior to transplant
- Involves long hospitalization
- Not a cure

- Marrow Transplant may be considered for some patients
Summary

1. **MDS** is not one disease, but a group of disorders that cause the bone marrow to fail.

2. **Diagnosis** may require a number of special tests on bone marrow and blood, and may need repeating before a firm diagnosis can be made!

3. **Treatments** range from ‘supportive’ to the ‘intensive’. Modern treatments, including BMT are, increasingly relevant to many patients with MDS.
MDS in Ireland

- Need for patient support group
- Resources needed for Irish MDS patients
- National MDS Registry
  - Information regarding incidence in Ireland
  - Diagnosis in older patients
  - Iron-overload problems
  - Issues related to diagnosis and management
  - Data on >300 patients