Myelodysplastic Syndrome

Dr. Anjali Kelkar  DNB(Pathology), IFCAP
Consultant - Diagnostic Haematology
NABL Assessor

Associate Professor in Pathology,
In-charge - Haematology Labs,
BVDU Medical College and Hospital, Pune.
Myelodysplastic Syndrome

- Dysplasia: a catchy description of what is essentially abnormal differentiation.

- Histologic hallmarks of aberrant hematopoietic cell differentiation
  - nuclear/cytoplasmic ratio,
  - nuclear shape,
  - agranularity
  - persistence of granules when they should be absent at that particular stage of differentiation

- Functional defects characteristic of abnormal differentiation:
  - Serious infections with normal neutrophil count
  - serious bleeding episodes despite reasonable platelet counts.
Myelodysplastic Syndrome

• Demonstration of altered differentiation:
  • In vitro: clonogenic assays
    • In vivo: gene expression defects in differentiation-related pathways
  
• Bone Marrow: Abnormal proliferation (hypercellular marrow):
  • abnormal differentiation: trigger of compensatory proliferation.

• Major difference between MDS and AML: high rate of apoptosis myelodysplastic cells

• Striking paradox: Clinically bone marrow failure syndrome, despite many of the hallmarks of a classical neoplasm (clonality, hypercellularity, progression to more advanced stages, etc).
Myelodysplasia

Diverse group of myeloid neoplasms

Characterised by:

Origin in somatically mutated multipotent haemopoietic stem cell

Ineffective haemopoiesis resulting in cytopenias with normocellular / hypercellular marrow: late precursor apoptosis

Clonal progression to AML
Case 1

- Male / 46
- Mild icterus
- Hb: 8.6
- TC: 3200
- PC: 98000
- MCV: 112
- LDH: 3800

Clinical Details, Trial of Haematinics
Presentations

Vary...

Indolent – mild to moderate anaemia

Multi-cytopenias

Leukaemia – Blasts ~ 20%
Clinical Features

- Asymptomatic
  - Mild anaemia / neutropenia / thrombocytopenia

- Loss of sense of well being
- Pallor
- Dyspnea on exertion
- Easy bruising / slow healing

- HSmegaly

- Hypothalamic malfunction, Sweet syndrome, Inflammatory syndromes
Stem Cell Division

Self Renewal to Maintain the Stem Cell Pool

Multiplication Mitotic Division

Differentiation: Progenitors of each cell lineage

Maturation

Function

Cell Death
Uncommitted stem cell gives rise to committed cells

proerythroblast  monoblast  myeloblast  lymphoblast  megakaryoblast

basophilic erythroblast  erythroblast  normoblast  reticulocyte

[a]  promyelocyte

[b]  neutrophil  basophil  eosinophil  lymphocyte  platelets

ererythrocyte  monocyte
<table>
<thead>
<tr>
<th>Year</th>
<th>Classification</th>
<th>Patients</th>
<th>Databases</th>
<th>Additional Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>IPSS/IMRAW (FAB)</td>
<td>816 pts</td>
<td>7 DBs</td>
<td>Marrow blasts, cytogenetics, cytopenias</td>
</tr>
<tr>
<td>2001</td>
<td>WHO classification</td>
<td></td>
<td></td>
<td>Dysplastic subgroups, RAEB-1,2, del(5q)</td>
</tr>
<tr>
<td>2007</td>
<td>WPSS</td>
<td>1165 pts</td>
<td>3 DBs</td>
<td>WHO subgroups, IPSS cytogenetics, RBC Txns</td>
</tr>
<tr>
<td>2001-2011</td>
<td>New features described as possible additional prognostic factors</td>
<td>2900 pts</td>
<td>4 DBs</td>
<td>New features described as possible additional prognostic factors</td>
</tr>
<tr>
<td>2011</td>
<td>IWG PM Refined consensus system (IPSS-R)</td>
<td>7012 pts</td>
<td>18 DBs</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCUD</td>
<td>Refractory cytopenia with unilineage dysplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RARS</td>
<td>Refractory anaemia with ringed sideroblasts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCMD</td>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCMD-RS</td>
<td>Refractory cytopenia with multilineage dysplasia and ringed sideroblasts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAEB-1</td>
<td>Refractory anaemia with excess blasts-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAEB-2</td>
<td>Refractory anaemia with excess blasts-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS-U</td>
<td>Myelodysplastic syndrome unclassified (MDS-U)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS del 5q</td>
<td>Associated with isolated 5q-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO</td>
<td>WHO 2008</td>
<td>Blood</td>
<td>Marrow</td>
<td>Survival</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------------</td>
<td>--------------------------------------</td>
<td>-------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>RA (5-10%)</td>
<td>Refractory cytopenias with unilineage dysplasia</td>
<td>Unicytopenia &lt;1% blasts</td>
<td>Unilineage dysplasia &gt;10% of the affected lineage are dysplastic &lt;5% blasts</td>
<td>66</td>
</tr>
<tr>
<td>RARS (10%)</td>
<td>Anaemia</td>
<td>Erythroid dysplasia only &lt;5% blasts, &gt;15% RS</td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>RCMD (24%)</td>
<td>Bi or pancytopenia</td>
<td>Dysplasia in at least 10% in more than 2 cell lines</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>RCMD-RS (15%)</td>
<td>Bi or pancytopenia</td>
<td>Dysplasia in more than 2 cell lines and &gt;15% ring sideroblasts</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>RAEB-1 (40% 1&amp;2)</td>
<td>Cytopenia &lt; 5% blasts Uni / multilineage dysplasia 5-9% blasts</td>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>Cytopenia 5-19% blasts</td>
<td>Uni / multilineage dysplasia 10-19% blasts or Auer rods</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>MDS-U</td>
<td>Cytopenias &lt;1% blasts</td>
<td>Unequivocal dysplasia in &lt;10% &lt;5% blasts</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>MDS del 5q (5%)</td>
<td>Anaemia; normal or increased platelets</td>
<td>Megakaryocytes with hypolobated nuclei &lt;5% blasts</td>
<td></td>
<td>116</td>
</tr>
</tbody>
</table>
## Minimal Diagnostic Criteria for Refractory Cytopenias of Childhood

<table>
<thead>
<tr>
<th></th>
<th>Erythropoiesis</th>
<th>Granulopoiesis</th>
<th>Megakaryopoiesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow aspirate</td>
<td>Dysplastic changes* and/or magaloblastoid changes in at least 10% of erythroid precursors</td>
<td>Dysplastic changes* in at least 10% of granulocytic precursor and neutrophils; &lt;5% blasts</td>
<td>Unequivocal micromegakaryocytes other dysplastic changes in variable numbers</td>
</tr>
<tr>
<td>Bone marrow Biopsy</td>
<td>A few cluster of at least 20 erythroid precursors. Stop in maturation with increased number of proerythroblast. Increased numbers of mitosis.</td>
<td>No minimal diagnostic criteria.</td>
<td>Unequivocal micromegakaryocytes; immunohistochemistry is obligatory (CD61, CD41), other dysplastic changes in variable numbers.</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td></td>
<td>Dysplastic changes at least 10% of neutrophils, &lt;2% blasts</td>
<td></td>
</tr>
</tbody>
</table>

* Abnormal nuclear lobulation, multinuclear cells, nuclear bridges,

* Pseudo-Pelger-Huet cells, hypo-or agranularity, giant bands (in cases of neutropenia this criteria may not be fulfilled).

* Megakaryocytes of variable size with separated nuclei or round nuclei. The absence of megakaryocytes will not exclude refractory cytopenia of childhood.
IPSS-R beyond IPSS

- Added refined cytogenetic subgroups (16 vs 7) & prognostic categories (5 vs 3)

- Analyzed depth of cytopenias

- Improved predictive power w/more precise prognostic subgroups (5 vs 4)

- Clear impact of age and additional predictive features for survival – PS, ferritin, LDH
Freedom from AML Transformation

IPSS

Months

N=7012

IPSS-R

Months

N=7012
Survival

Survival curves for IPSS and IPSS-R with different risk categories:

- **IPSS**
  - LOW
  - INT-1
  - INT-2
  - HIGH

- **IPSS-R**
  - Very good
  - Good
  - Intermediate
  - Poor
  - Very poor

N=7012

Months
The Molecular Life Cycle of MDS in Stepwise Multi-hit Theory
Possible initiating mutations

5q deletion

Haploinsufficiency for miR-145 & miR-146a
  Upregulated target genes
    Thrombocytosis

Haploinsufficiency RPS14
  p53 activation
    Activation of p53 target genes
      Erythroid defect

5q- syndrome

Additional mutations

Additional karyotypic abnormalities

AML
Pathogenesis

Hypercellular bone marrow and peripheral blood cytopenias

- Primary or acquired DNA damage to haemopoietic precursor cell leads to myelodysplastic clone

- Immune damage and increased apoptosis leads to damage of both the clonal and normal haematopoietic cells

- (expanded T-cell population – which can sometimes result in T-cell LGL leukaemia).
The myelodysplastic syndrome as a prototypical epigenetic disease

Jean-Pierre J. Issa

Updated information and services can be found at:
http://bloodjournal.hematologylibrary.org/content/121/19/3811.full.html

Articles on similar topics can be found in the following Blood collections
- Clinical Trials and Observations (3846 articles)
- Myeloid Neoplasia (1172 articles)
- Review Articles (506 articles)
- Review Series (25 articles)
Epigenetics...

Stable, long-term regulation of gene expression that is unrelated to variation in the DNA coding sequence and that can survive across numerous rounds of cell division.

DNA methylation, Post-translational histone tail modifications, Micro-RNA expression
The myelodysplastic syndrome as a prototypical epigenetic disease..

MDS is a disease of disordered differentiation
Differentiation is an epigenetic process
MDS cells carry an abnormal epigenome
MDS shows frequent epigenetic effector mutations
MDS responds to epigenetic therapy - Azacitidine, Decitabine
Oncogene activation at the transition of MDS to AML
Evidence of Clonality

G6PD mosaicism

Cytogenetic studies: studies revealing clones with and without trisomy 8 in patients with sideroblastic anemia

RFLPs of X-chromosome genes

FISH

Evidence of clonality in lymphoid lineages: the MDS clone arises from early pluripotent stem cells capable of myeloid and lymphoid differentiation.

Karyotypic evolution and complex karyotypic changes with the evolution of many “escape” clones may occur with progression of MDS and transformation to AML.
A model of MDS formation and progression

Normal stem cell → Aberrant epigenetic programs → Normal, trilineage differentiation

MDS stem cells → Aberrant growth signals & reduced apoptosis → Trilineage dysplasia, compensatory stem cell expansion and increased apoptosis

Epigenetic Modifications

NRAS

AML → Inhibited differentiation and uncontrolled blast cell proliferation
Pathogenesis

Thought to overlap with
PNH,
Aplastic anaemia
T-LGL leukaemia

Aplastic anaemia – cytogenetic abnormalities rare at diagnosis.

– 30% by 3 years and 12% develop MDS by 12 years.
Predisposing Factors & Epidemiologic Associations

**Heritable predisposition**
Constitutional genetic disorder: Down Syndrome, Trisomy 8, Familial monosomy 7, Neurofibromatosis 1
Germ cell tumours (embryonal dysgenesis)
Congenital neutropenia (Kostmann or Shwachman-Diamond Syndrome)
DNA repair deficiencies: Fanconi anemia, Ataxia telangiectasia, Bloom syndrome, Xeroderma pigmentosum

**Mutagen detoxification (GST q1-null)**

**Acquired**

**Senescence**

**Mutagen exposure**

Genotoxic therapy: Alkylators, Topoisomerase II inhibitors, phosphorus-32, Autologous BMT
Environmental or occupational exposure (eg; benzene)
Tobacco

Aplastic anemia, PNH, MPN
Epidemiology

Median age 69
   Age 40 yrs : 0.2/100,000
   Age 85 yrs : 45/100,000

Male : Female :: 1.5:1

Younger adults : Usually preceded by chemoRx / irradiation

Children :
   5 to 15 yrs : 0.1/100,000
   More advanced type
   Predisposing inherited condition : e.g. Fanconi anaemia
Laboratory Features

Anaemia:
- Macrocytic
- Anisocytosis
- Anisochromia
- Basophilic Stippling
- nRBC - rare
Laboratory Features

Neutropenia
Pseudo Pelger-Huet
Hypogranularity
Monocytosis
Thrombocytopenia

Thrombocytosis
Diagnosis

History

Prior exposure to chemo/ radiation

FH of AML/ MDS

Infections, bleeding, bruising

CBC and peripheral blood film

S.Ferritin, B12, folate
Diagnosis

BM Aspirate:

*BM study: Not always indicated if not going to change treatment*

- At least 200 marrow cells and 20 megakaryocytes should be examined
- Dysplastic features in at least 10%
- Pseudo-pelger neutrophils, ring sideroblasts, micromegakaryocytes and blasts correlate strongly with clonality

- Neutrophil granularity: variations in stain quality
Diagnosis

**BM Trephine biopsy**
- Should be done if BM indicated
- ALIPs are prognostic
- Allows assessment of cellularity

**BM Cytogenetics**
- Confirms clonalility
- Prognostic implications
You thought I was asleep, didn´t you?

Acting.
Exclude
Megaloblastic
HIV
Alcohol
Recent cytotoxic Rx
Severe intercurrent illness
## MDS / MPD International Prognostic Scoring System

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMML</td>
<td>M &gt;1</td>
<td>Dysplasia in one or more myeloid line</td>
</tr>
<tr>
<td></td>
<td>BCR-ABL neg</td>
<td>&lt;20% blasts</td>
</tr>
<tr>
<td></td>
<td>&lt;20% blasts</td>
<td></td>
</tr>
<tr>
<td>Atypical CML (BCR-ABL negative)</td>
<td>Neutrophil dysplasia</td>
<td>Neutrophil dysplasia</td>
</tr>
<tr>
<td></td>
<td>Neutrophil precursors &gt;10%</td>
<td>&lt;20% blasts</td>
</tr>
<tr>
<td></td>
<td>leucocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blasts &lt;20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monocytes &lt;10%</td>
<td></td>
</tr>
<tr>
<td>JMML</td>
<td>M &gt;1</td>
<td>&lt; 20% blasts</td>
</tr>
<tr>
<td></td>
<td>&lt;20% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wbc &gt;10</td>
<td></td>
</tr>
<tr>
<td>MDS/ MPNu</td>
<td></td>
<td>&lt; 20% blasts</td>
</tr>
<tr>
<td>RARS-T (with thrombocytosis)</td>
<td>Plts &gt;450</td>
<td>As per RARS</td>
</tr>
<tr>
<td></td>
<td>Anaemia</td>
<td>Abnormal megakaryocytes</td>
</tr>
<tr>
<td>Cytogenetic prognostic subgroups</td>
<td>Cytogenetic abnormalities</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>-Y, del(11q)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(5q), del(12p), del(20q), double including del(5q)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>del(7q), +8, +19, i(17q), any other single or double independent clones</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities</td>
<td></td>
</tr>
<tr>
<td>Very poor</td>
<td>Complex: &gt;3 abnormalities</td>
<td></td>
</tr>
<tr>
<td>Prognostic variable</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Very Good</td>
<td>Good</td>
</tr>
<tr>
<td>BM Blast %</td>
<td>&lt;=2</td>
<td>&gt;2-&lt;5%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt;=10</td>
<td>8-&lt;10</td>
</tr>
<tr>
<td>Platelets</td>
<td>&gt;=100</td>
<td>50-&lt;100</td>
</tr>
<tr>
<td>ANC</td>
<td>&gt;=0.8</td>
<td>&lt;0.8</td>
</tr>
</tbody>
</table>
### IPSS-R Prognostic Risk Categories/Scores

<table>
<thead>
<tr>
<th>RISK CATEGORY</th>
<th>RISK SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>( \leq 1.5 )</td>
</tr>
<tr>
<td>Low</td>
<td>( &gt;1.5 - 3 )</td>
</tr>
<tr>
<td>Intermediate</td>
<td>( &gt;3 - 4.5 )</td>
</tr>
<tr>
<td>High</td>
<td>( &gt;4.5 - 6 )</td>
</tr>
<tr>
<td>Very High</td>
<td>( &gt;6 )</td>
</tr>
</tbody>
</table>
Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndromes Risk Assessment Calculator

Developed by the International Working Group for the Prognostic of MDS (IWG-PM) under the aegis of the MDS Foundation, Inc.

When entering values into the calculator, note the units given in parentheses. Also note that the usual ranges, given for orientation, are in brackets. These are not normal ranges.
## MDS v/s SAA

<table>
<thead>
<tr>
<th>Haemopoietic Inhibitors</th>
<th>MDS</th>
<th>SAA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early stages</td>
<td></td>
</tr>
<tr>
<td>Progenitor Cells</td>
<td>In low-risk groups</td>
<td>Marked</td>
</tr>
<tr>
<td>Marrow cells Apoptosis</td>
<td>In low-risk groups</td>
<td>Marked</td>
</tr>
<tr>
<td>Telomere Shortening</td>
<td>Present</td>
<td>Marked</td>
</tr>
<tr>
<td>Clonal Haemopoiesis</td>
<td>Yes</td>
<td>Rare (Except PNH)</td>
</tr>
<tr>
<td>G and GM CSF Production</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hypocellular MDS vs. AA

Hypocellular MDS responds better to immuno-suppressive therapy than normocellular MDS

*Erythroid dysplasia is found in AA and cannot be used to distinguish*

*Abnormal karyotype favours MDS but not 100%*
Specific Syndromes

Clonal Sideroblastic Anaemia
Clonal Non-Sideroblastic Anaemia
Clonal Multicytopenia with Hypercellular Marrow
The 5q- Syndrome
Monosomy 7 Associated Syndromes
Oligoblastic Myeloid Leukemias
Therapy related MDS
Theodor Boveri
(12 October 1862 – 15 October 1915)

HOME :: CHAPTER 7
Theodor Boveri: The Life of a Great Biologist 1862-1915
The Chromosome Theory of Inheritance, Experiments with Double Fertilized Sea Urchin Eggs (Dispermy Experiments)
5q- Syndrome

F>M

Severe anaemia, erythroblastopenia

Thrombocytosis

Typical dysmegakaryopoiesis

Favourable outcome

Progression to AML is rare (10%)

Previously iron overload was a major problem
**5q- Syndrome**

Lenalidomide results in transfusion independence in 2/3, and in 2/3 responses persist after 2 years

Complete pathological and cytogenetic responses may also be achieved

Grade 3 or 4 neutropenia and thrombocytopenia

Preliminary results suggest Lenalidomide also active in 5q- with other cytogenetic abnormalities or >5% blasts
Ribosomopathies: Etiology in 5q-

- Distinct mutations in the ribosome biogenesis pathway
- Haploinsufficiency of ribosomal proteins (RPs)
- Reduced mRNA translation

Bone marrow failure

Figure 1: Ribosome Structure and Function in Protein Synthesis
Ribosomopathies: Etiology in 5q

Zebrafish models demonstrate the relationship between haploinsufficiency of rps14 and profound anaemia.

Treatment with mRNA translation activator L-Leucine amino acid results in marked improvement of anaemia.
Lenalinomide

Immunomodulatory drug

Suppression of pro-inflammatory cytokine production

Enhancement of T and NK cell activation

Anti-angiogenic and anti-TNF properties

Non-teratogenic in animal models, but pregnancy still contraindicated

Doesn’t lead to peripheral neuropathy
Lenalinomide

Landmark paper by List et al

Lenalidomide gave an erythroid response in 50% of transfusion dependant low risk MDS
83% in patients with del 5q
Large phase II trial of Lenalidomide and 5q-
67% achieved transfusion independence
Median time to independence 4 weeks
Complete cytogenetic response in 45%
Grade 3 or 4 myelosupression in about 50%, tended to improve after 6-8 weeks

Studies combining Lenalidomide and other drugs (esp EPO) in low risk MDS with anaemia are in progress
Monosomy 7 associated syndromes

Common cytogenetic abnormality in MDS
Post Chemo / Radiation
Commonly transformed to AML
In children: Atypical myeloproliferations
Case 2

42 / F

Operated case of Ca Breast 3 years ago

Received treatment with Doxorubicin (Topoisomerase II inhibitor)

Now presents with

- Hb 6.9
- TC 4100 ANC 1200
- PC 110000
- No organomegaly
- LDH 320
Therapy related MDS

t-MN approximately 10 to 20 percent of all cases of AML, MDS, and MDS/MPN.

Incidence varies according to the underlying disease, specific agents, timing of exposure, and dose.

Median age at diagnosis: 60 years.

?? heritable predisposition in some patients.
MDS and α Thalassemia

Acquired Alpha thalassemia is the best characterized of the acquired red blood cell disorders in patients with hematologic malignancy.

Almost always associated with a myelodysplastic syndrome.

Molecular mechanisms:
Acquired deletion of the alpha-globin gene cluster limited to the neoplastic clone.

Inactivating somatic mutations of the trans-acting chromatin-associated factor ATRX, which cause dramatic down-regulation of alpha-globin gene expression.
<table>
<thead>
<tr>
<th>Survival</th>
<th>Age &lt;60</th>
<th>Age &gt;60</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk = 0</td>
<td>11.8</td>
<td>4.8</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Intermediate risk 1 = 0.5 – 1</td>
<td>5.2</td>
<td>2.7</td>
<td>Age &lt;65 SCT work up (non ablative if &gt;50)</td>
</tr>
<tr>
<td>Intermediate risk 2 = 1.5 – 2</td>
<td>1.8</td>
<td>1.1</td>
<td>Chemotherapy and SCT if respond (non responders have very poor prognosis)</td>
</tr>
<tr>
<td>Poor risk = &gt;2</td>
<td>0.3</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>
Treatment decisions on the basis of IPSS

Supportive care

Either for patients with good prognosis or poor prognosis when age or comorbidity prevent other treatments

Anaemia

Up to 80% have HB <10 at diagnosis

Transfusion and iron chelation

Chelation once received 5g iron (25 transfusions) and likely to need long term transfusion support

Audiometry and ophthalmology before desferrioxamine and annually

Target ferritin < 1000

Desferrioxamine at time of transfusion has no basis

Oral iron chelators now a possibility
Treatment decisions on the basis of IPSS

**Epo +/- GCSF**

RA or RAEB, symptomatic of anaemia, with no/low transfusion requirement (<2/month) and a basal epo of < 200 be considered for a trial of Epo at 10,000 daily for 6 weeks

Non-responders, add GCSF or double dose of Epo

GCSF escalated weekly 75-150-300 to maintain wbd between 6-10

RARS, symptomatic anaemia and basal epo <500, transfusion <2/month

Combined Epo and GCSF from outset
Treatment decisions on the basis of IPSS

**Immunosuppression**

ALG/ CsA

Hypoplastic MDS and PNH

Thrombocytopenia

Platelet support

Antifibrinolytics

§ Infection

§ Prophylaxis

§ No evidence for prophylaxis

§ Consider GCSF to keep neutrophil >1
Non-intensive Chemotherapy

CMML

Hydroxyurea is preferred to oral Etoposide

5-Azacytidine and Decitabine show promise

27% with RA and RARS achieved a CR or PR with INT-1 MDS with Aza

14% with Decitabine

Multiple courses are required with a median time to response of 2-4 months

Duration of response generally <1 year

Preliminary analysis of a large trial (>200) with non 5q-, low IPSS MDS treated with Lenalidomide reported transfusion independance in 25%

In older patients, unsuitable for transplant 5-aza and decitabine can be considered

Newer agents such as Clofarabine have shown promise
Intensive Chemotherapy or SCT

- Long term EFS in 32-54% in those eligible
- Improved outcome
  - Younger age
  - Shorter disease duration
  - HLA compatibility
  - Primary MDS
  - <10% blasts
  - Good risk cytogenetics
Intensive Chemotherapy or SCT

IPSS low
Not recommended as median survival without treatment is 5 and 12 years (>60 and <60 years)

IPSS Int 1
<65 years
Assessed for SCT ASAP
<50 years and sibling donor, ablative SCT
50-65, non-ablative
Intensive cytoreductive therapy prior to SCT is not recommended
Intensive Chemotherapy or SCT

- IPSS Int 2/ high
- Chemotherapy plus SCT
- SCT only for those who respond to remission induction chemotherapy
- Outcome for non-responders very poor
- For those without a sibling or matched donor, consider auto
- Chemotherapy alone
- >65 or younger but not eligible, consider intensive chemo alone
- Most have 2 courses
Case 3

M / 62

Presented with malaise

O/E Pallor, Mild splenomegaly

No lymphadenopathy

Hb 8.1, TC 2800, ANC 700, PC 62000

Bone marrow study: Blasts 04%. Features of dysplasia present in all three cell lineages. No ringed sideroblasts seen.

Diagnosis on BM: RCMD

Cytogenetics: Complex Karyotype
How will you score this patient?
What is the prognosis?
What could be the line of treatment?
Ok...Just write "Funny looking cells in pink and violet. Correlate clinically ".

PATHOLOGY
Thank you!