MDS: Understanding your diagnosis and current and emerging treatments

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Disclosures

- Nothing to disclose.

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Objectives

- Understand what is MDS
- Understand the symptoms, signs and diagnosis of MDS
- Standard treatment options for MDS
- How you can help with management of your disease

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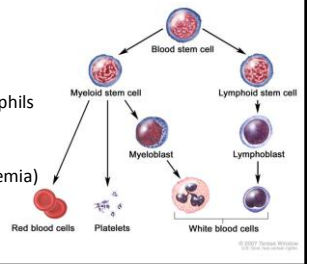
Normal blood cells production

- Hematopoietic "blood-forming" stem cells
- They produce all the
  - White blood cells: neutrophils (if low → neutropenia), lymphocytes, etc
  - Red blood cells (if low anemia)
  - Platelets (if low thrombocytopenia)



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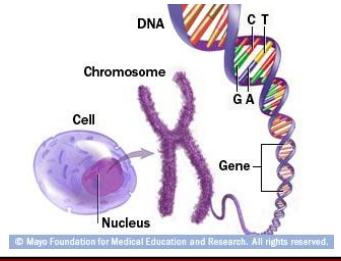
Story of DNA



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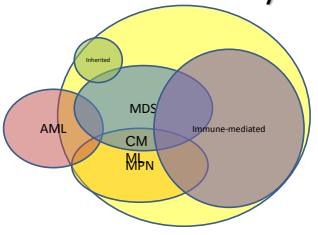
Bone marrow failure syndromes



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What is MDS

- MDS is a malignant blood disease
- MDS is a form of bone marrow failure
- Stem cells do no mature as they should → ineffective blood production

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Myeloproliferative neoplasms (MPN)

- Polycythemia vera
- Essential thrombocythemia
- Chronic myeloid leukemia (CML)
- Primary myelofibrosis

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Chronic myelomonocytic leukemia (CMML)

- Malignant stem cell disorder with clinical and pathological features of both a myeloproliferative neoplasm (MPN) and myelodysplastic syndrome (MDS).
- Characterized by a peripheral blood monocytosis, bone marrow dysplasia; cytopenias and hepatosplenomegaly.
- High rate of transformation to AML

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MDS- Symptoms

- Some have no symptoms, discovered on routine blood work
- Anemia (low hemoglobin or low red blood cells) → fatigue, pale, trouble breathing, chest pain, rapid heart beat
- Low neutrophils → increased infections
- Low platelets → easy bleeding/bruises

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MDS commonly occur in older patients

- Average age at diagnosis 71-76 years
- 12,000-15,000 new cases/year
- 50,000 to 75,000 people currently live with MDS in the US
- Can have a slow course ---- more aggressive course
- 1/3 progress to acute myeloid leukemia (AML)

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Causes and Risk factors

- De Novo MDS:
  - Increasing age
  - Occupational and environmental exposures: e.g. benzene, pesticides
  - Genetic syndromes
  - Male gender
- Treatment-related MDS:
  - Previous chemotherapy
  - Radiation

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How is MDS diagnosed?

- Medical history
- Physical exam
- Lab studies: CBC (complete blood counts), B12, folic acid, iron, EPO level
- Bone marrow biopsy

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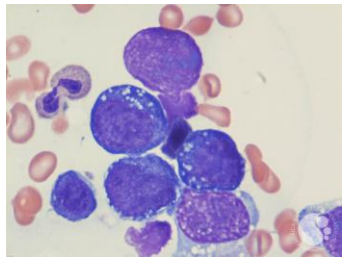
Bone marrow biopsy



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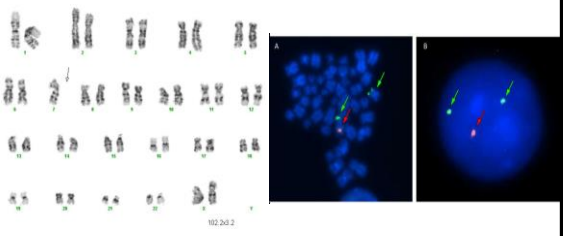
Timothy C Carll, MD; Girish Venkataraman, MD, MBBS
ASH image bank

Cytogenetics and FISH



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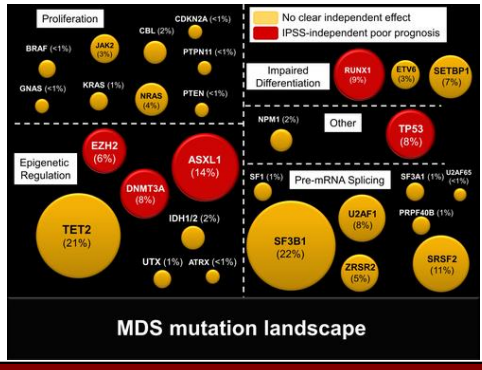

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Slide courtesy of Steensma and Morgan

Classification of MDS

- WHO classification
- IPSS: international prognostic group classification
- IPSS: revised international prognostic group classification

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WHO (World Health Organization) Classification System

MDS Subtype	Blood Findings	Bone Marrow Findings
RCUD (Refractory Cytopenia with Unilineage Dysplasia) Note: Considered the mildest category. MDS is limited to one cell line. There is little dysplasia.	Has 3 subtypes: •RA (Refractory Anemia) •RN (Refractory Neutropenia) – Low white cell count •RT (Refractory Thrombocytopenia) – Low platelet count	Less than 5 percent young blood cells (blasts) – applies to RA, RN and RT •Red cell dysplasia (cells with an abnormal size, shape, or look) •White cell dysplasia •Megakaryocyte dysplasia
RARS (Refractory anemia with ring sideroblasts)		In RARS, more than 15 percent red blood cells that contain ring-shaped iron deposits (ring sideroblasts)
RCMD (Refractory Cytopenia with Multilineage Dysplasia)	Low white blood cell count (neutropenia) or low platelet count (thrombocytopenia)	Dysplasia in more than 1 cell type Less than 5% blasts, or less than 15% ringed sideroblasts
RAEB-1 (Refractory Anemia with Excess Blasts)	The same as refractory anemia	5% tp 9% blasts in marrow
RAEB-2 (Refractory Anemia with Excess Blasts 2)	Similar to refractory anemia	10% to 19% blasts in marrow May have blasts in blood
Isolated Del 5q (Deletion 5q)	The same as refractory anemia, plus normal or high platelet count	Deletion of chromosome 5q, with no other chromosome abnormality
RCC (Refractory cytopenia in childhood)	Often more than one low blood count.	Bone marrow is often empty of cells (hypocellular) This is rare
Unclassified MDS	Low count for wither platelets or white blood cells	Unusual features, such as scarring (fibrosis) of the bone marrow Note: Just 1% to 2% of MDS patients have this subtype

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IPSS-R

Prognostic variable	Score						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast	<2%		>2% to <5%		5% to 10%	>10%	
Hemoglobin	≥10		8 to <10	<8			
Platelets	≥100	50 to 100	<50				
ANC	≥0.8	<0.8					

Cytogenetic definitions:
Very good: -Y, del(11q).
Good: Normal, del(5q), del(12p), del(20q), double including del(5q).
Intermediate: del(7q), +8, +19, i(17q), any other single, double not including del(5q) or -7/del(7q), or independent clones.
Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities.
Very poor: Complex: >3 abnormalities.

Risk group	IPSS-R score	Median overall survival (years)	Median time to 25% AML evolution (years)
Very low	≤1.5	8.8	>14.5
Low	>1.5 to 3.0	5.3	10.8
Intermediate	>3 to 4.5	3.0	3.2
High	>4.5 to 6	1.6	1.4
Very high	>6	0.8	0.7

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Treatments: factors to consider

- Your symptoms
- Your age
- Which subtype of MDS you have
- Your IPSS or IPSS-R (International Prognostic Scoring System) disease risk score
- Other serious conditions or diseases you have
- Whether someone is willing and able to donate matching bone marrow to you

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Treatment: Goals

- Improve quality of life
- Improve survival
- Avoid complications
- Reduce progression to AML

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Treatment: general approaches

1. Wait and watch, which might be suggested if your blood counts are not too low and your symptoms are not too bad
2. Supportive care to help you manage the symptoms of your MDS
3. Drug Therapy with medicines specifically approved to treat MDS and stop abnormal cells from growing
4. Immunosuppressive therapy, which can lower your body's immune response
5. Chemotherapy, using drugs that kill abnormal cells
6. Bone marrow transplantation to replace damaged bone marrow stem cells with healthy ones

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Transfusions

- Red blood cells often necessary
- May range from 1 unit every 4-12 weeks to 1-2 units per week
- Improve quality of life
- Repeated red cells transfusions can lead to iron overload
- Transfusion of platelets may also be needed

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Iron Overload

- After approximately 20 units of RBC
- Can accumulate in liver, heart, and other organs
- Iron chelation may be needed
  - Desferal (Deferoxamine): IV or subcutaneous
  - Ferriprox (Deferiprone): oral, can cause low WBC
  - Exjade or Jadenu (Deferasirox): oral, can cause kidney or liver failure or GI bleeding

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Growth factors

- Engineered natural hormones
- ESA: like Epogen or Procrit (Retacrit is a new biosimilar) may help if epo level is low
- GCSF or granulocyte colony stimulating factor or neupogen or neulasta

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Lenalidomide (Revlimid)

- Used in low risk MDS with deletion of 5q
- Oral
- Daily for 3 weeks then 1 week off
- Modulates the immune system
- Can cause blood clots, fatigue

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Hypomethylating agents

- Azacitadine, subcutaneous for 7 days
- Decitabine, IV for 5 days
- About a third to half the patients will have some response
- Compared to supportive care, longer time to AML and improved quality of life.
- Side effects include nausea, diarrhea and fatigue

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Stem cell transplant

- Only potential cure for MDS
- It has significant toxicity but improved techniques such as reduced intensity transplants allowed successful transplants in the 7^{th} and 8^{th} decade of life.
- Risk vs benefit should be carefully reviewed for each individual particularly in lower risk MDS.

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What can you do?

- Be a full partner in your care.
- Know your blast count, blood counts, risk group
- Ask about different treatment options
- Ask about clinical trials (clinicaltrials.gov)
- Ask for help: family, friends, AAMDSIF, MDS Foundation, Leukemia and Lymphoma Society.

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Things you can do to manage symptoms

- Fatigue (anemia)
  - Allow rest periods.
  - Good night sleep
  - Delegate tasks
- Bleeding (low platelets)
  - Use a soft toothbrush
  - Electric razor
  - Avoid clutter

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Things you can do to manage symptoms

- Infection (low white cells)
  - Good hand washing
  - Don't share utensils or drinking glasses
  - Eat foods that are washed and well cooked
  - Avoid crowds
  - Monitor temperature
  - Take antibiotics as prescribed

Questions