UNIVERSITY of MARYLAND MEDICAL CENTER

Myelodysplastic Syndromes

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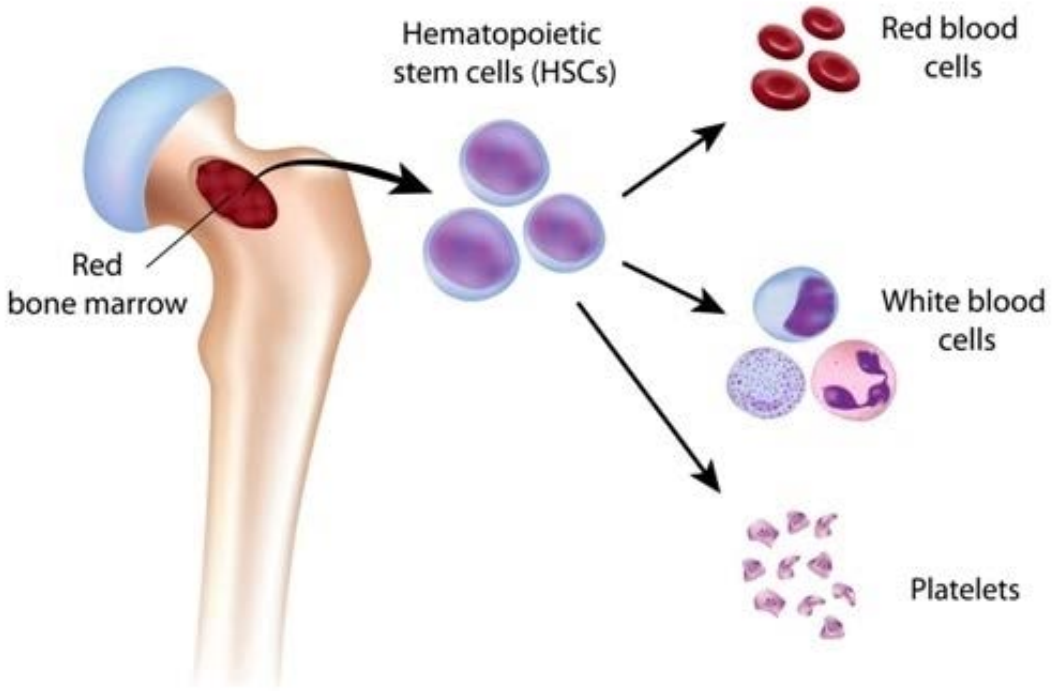
Our To Do List For Today

- How We Make Blood
- Where Does Cancer Comes From?
- Myelodysplastic Syndrome
  - Diagnosis
  - Prognosis
  - Treatment
  - Future Treatments in Development
  - Preparing for Your Clinic Appointments

Our To Do List For Today



What is the Bone Marrow?

- Soft tissue within bone cavities
- Produces blood cells and stores fat
- Can generate hundreds of billions of new blood cells every day
- There are a lot of blood vessels

Source: https://www.news-medical.net/life-sciences/Hematopoiesis-Process.aspx

How Do We Make Blood?

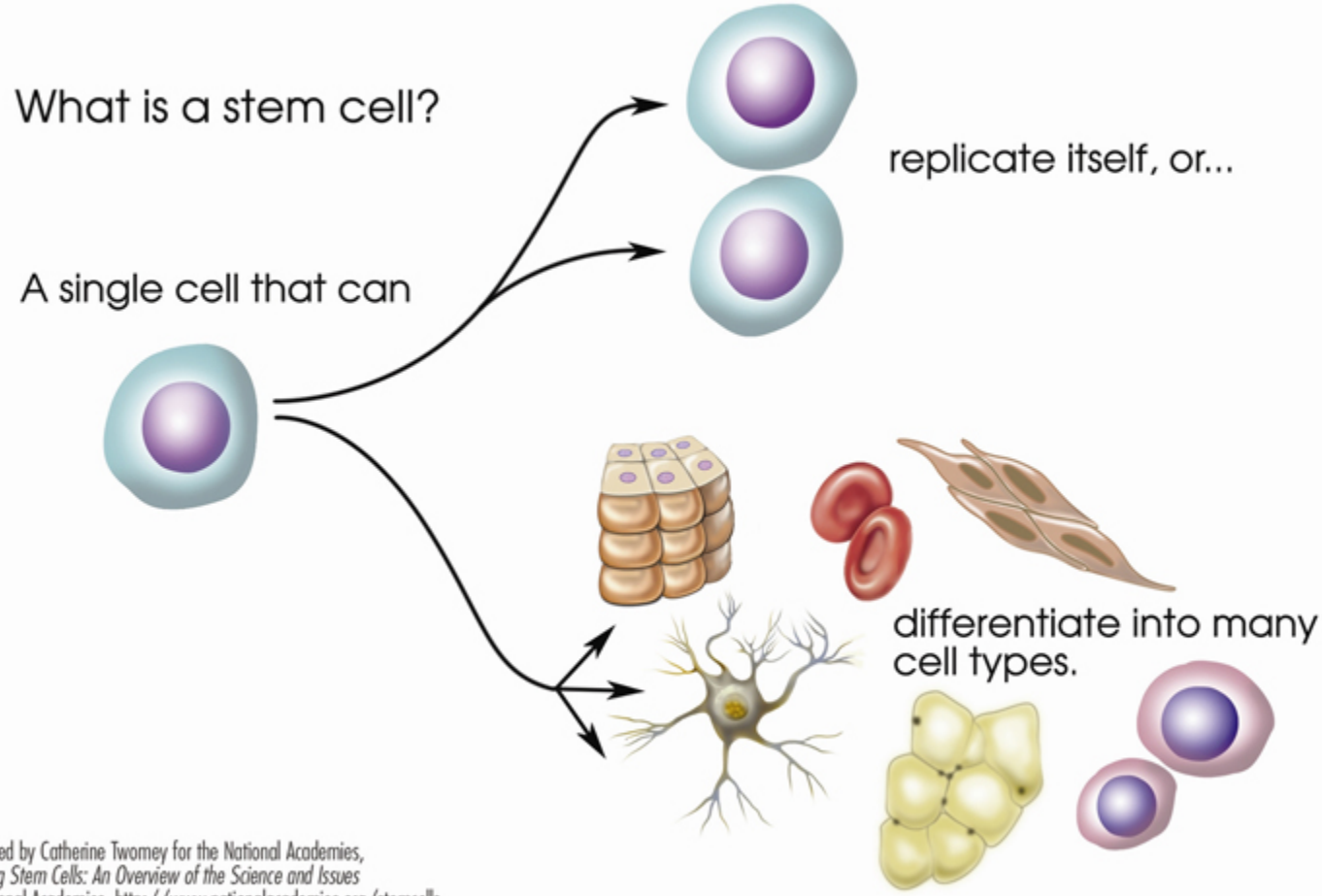
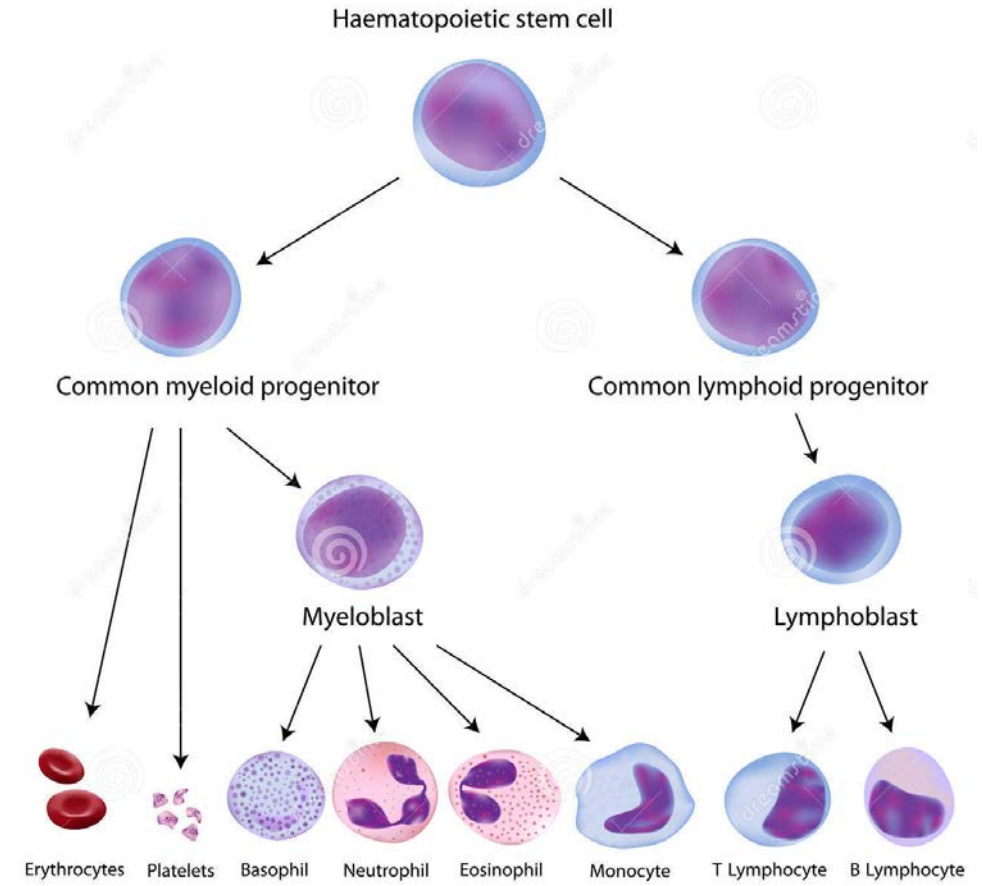


Image prepared by Catherine Twomey for the National Academies, *Understanding Stem Cells: An Overview of the Science and Issues* from the National Academies, http://www.nationalacademies.org/stemcells. Academic noncommercial use is permitted.

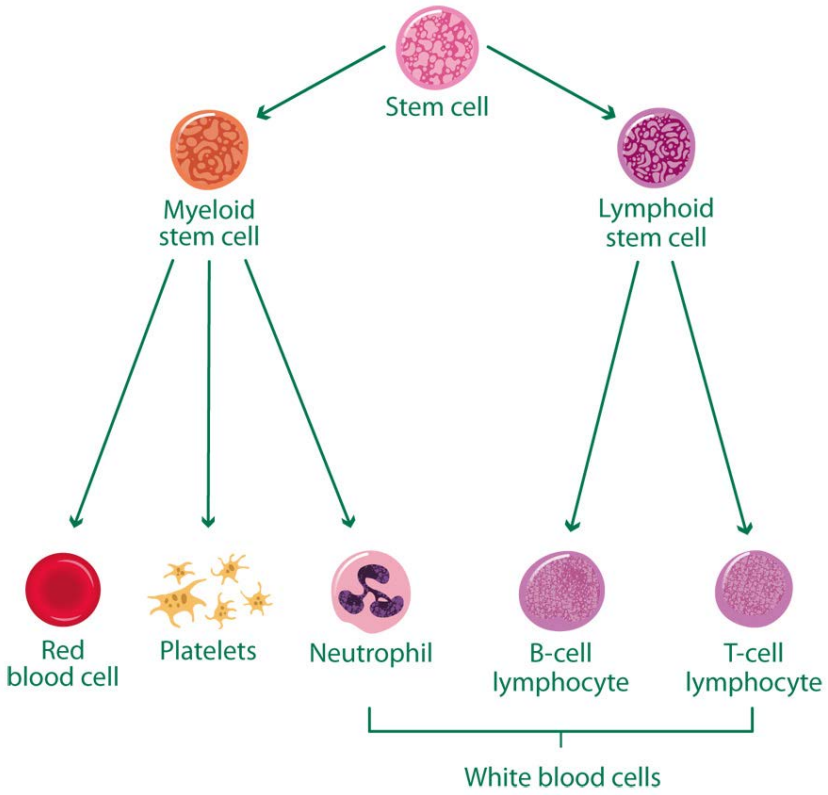
Bone Marrow Stem Cells



How Do We Make Blood?

Myeloid Stem cells

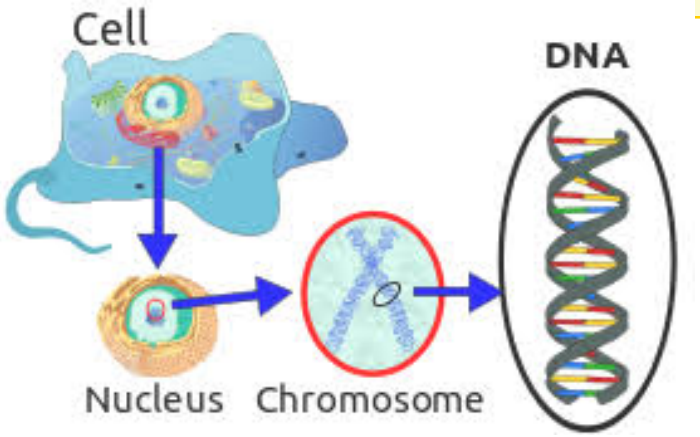
- Develop into **myeloblasts** or "**blasts**" which eventually develop into white blood cells
- **Blasts** cells are new, very young (immature) blood cells that grow into adult (mature) blood cells over time.
- Different **blast** cells become different types of mature blood cells
- Once blood cells are mature, they leave the bone marrow and enter the bloodstream to do their jobs

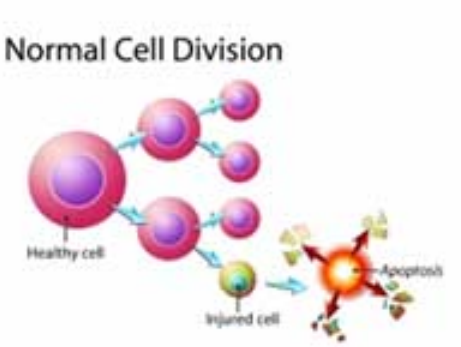


What is Myelodysplastic Syndrome (AKA MDS)

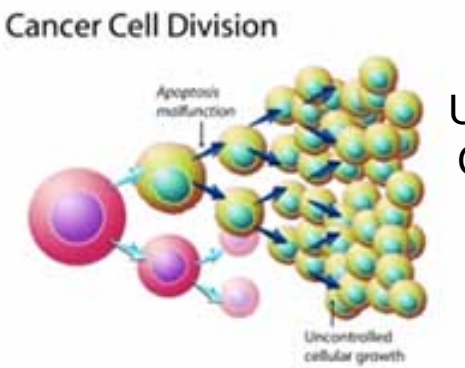
- MDS is a group of malignant bone marrow stem cell cancers
  - Atypical appearing cells (cytologic dysplasia)
  - Impaired maturation (ineffective hematopoiesis)
  - Low blood counts (cytopenias)
- MDS is a cancer
- Increased risk of progression to acute myeloid leukemia (AML), an aggressive blood cancer

Cancer Cell Growth





Death of cell



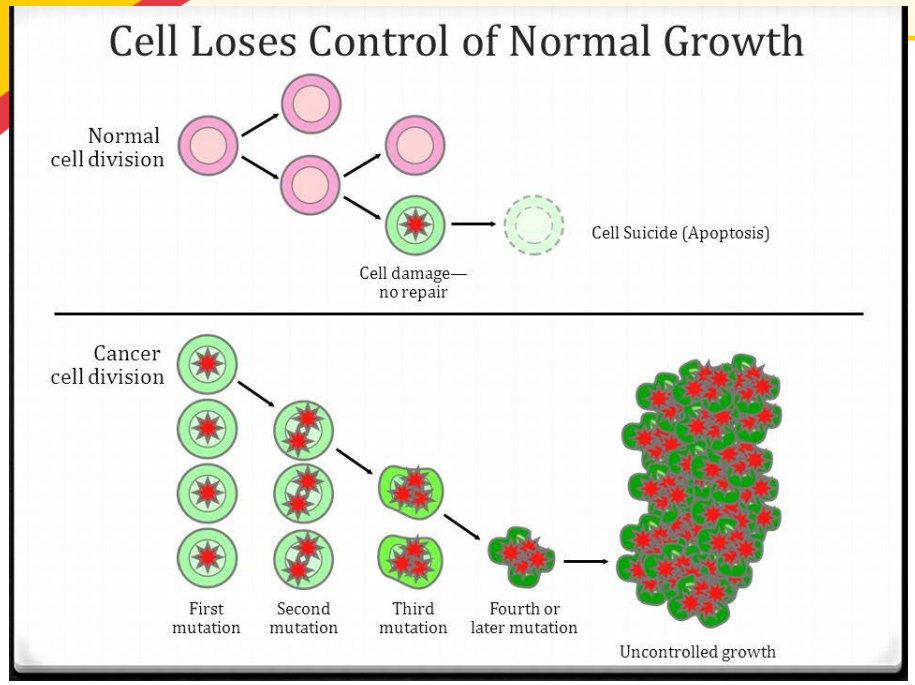
Uncontrolled Cell Growth Leads to ***cancer***

- Inside all cells are instructions for building new cells and controlling how cells are made and behave. These instructions are called **genes**.
- **Genes** are a part of our DNA
- DNA is grouped together in long strands called **chromosomes**
- These **chromosomes** in cancer cells are examined using FISH or cytogenetics as part of the bone marrow biopsy diagnosing MDS.

- We all have myeloblasts or lymphoblasts
- Changes or mutations in genes can cause normal ***myeloblasts*** or ***blasts*** to ***become cancer cells***
- Researchers are working to learn what causes **genes** to change and cause cancer.

Courtesy: https://www.anylogic.com/resources/articles/the-effect-of-cellular-interactions-on-cancer-cell-growth-using-evolutionary-game-theory/

Cancer Cells versus Normal Cells



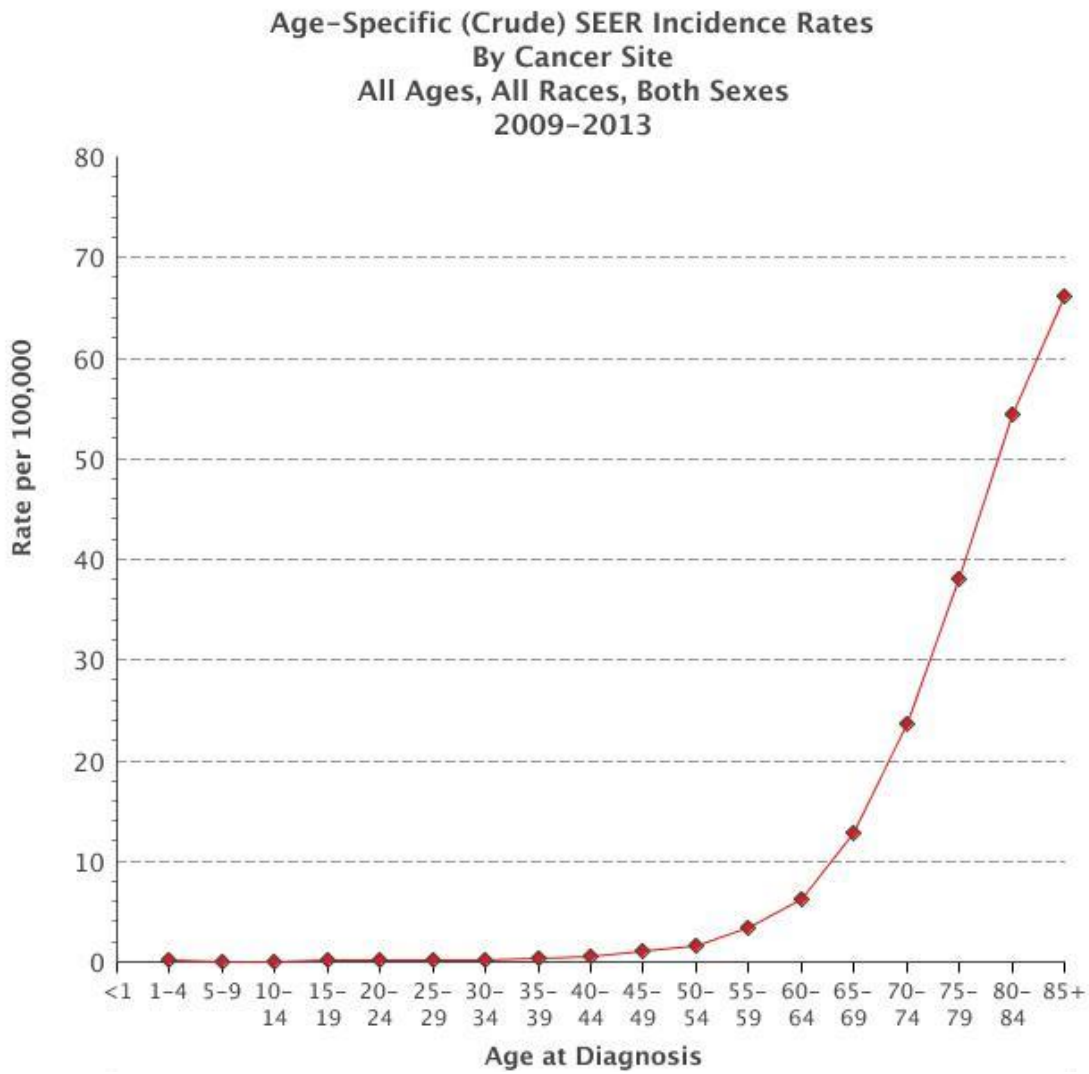
Abnormal ***myeloblasts*** ("***blasts***") are the cancer cells resulting in MDS

MDS Cancer Cells vs Normal cells

- ***Blasts*** grow more quickly and live longer than normal cells
- ***Blasts*** divide and copy themselves to make more blasts
- ***Blasts*** cells can spill out of the bone marrow into the blood stream. They can spread to other parts of the body including collecting in the spleen, thymus, lymph nodes, liver, testicles, skin, and area around the brain and spinal cord.

Image Courtesy of National Cancer Institute

Age and MDS



Average age at diagnosis:

~75 years old

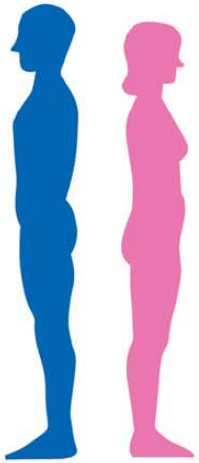
http://seer.cancer.gov/faststats/ Accessed July 1, 2016

Statistics

- Slight male predominance
- Annual incidence in the US: 3.3 per 100,000 people (~10,000 new cases/year)

Estimated New Cases

Males				Females		
Prostate	180,890	21%		Breast	246,660	29%
Lung & bronchus	117,920	14%		Lung & bronchus	106,470	13%
Colon & rectum	70,820	8%		Colon & rectum	63,670	8%
Urinary bladder	58,950	7%		Uterine corpus	60,050	7%
Melanoma of the skin	46,870	6%		Thyroid	49,350	6%
Non-Hodgkin lymphoma	40,170	5%		Non-Hodgkin lymphoma	32,410	4%
Kidney & renal pelvis	39,650	5%		Melanoma of the skin	29,510	3%
Oral cavity & pharynx	34,780	4%		Leukemia	26,050	3%
Leukemia	34,090	4%		Pancreas	25,400	3%
Liver & intrahepatic bile duct	28,410	3%		Kidney & renal pelvis	23,050	3%
All Sites	**841,390**	**100%**		**All Sites**	**843,820**	**100%**



- Few risk factors identified: exposure to chemicals, radiation, tobacco, or chemotherapy, genetic abnormalities

1. Rollison DE, Blood 2008;112:45-52
2. Seigel RL. CA Cancer J Clin 2016;66:7-30

Signs/Symptoms

- Discovered incidentally or after a blood count is drawn due to symptoms, including:
  - Fatigue, weakness, shortness of breath (anemia)
  - Infections (neutropenia)
  - Bleeding (thrombocytopenia)
  - Skin rash/petechia, bruising

- Low blood counts (cytopenias) on blood work:
  - Low hemoglobin, Anemia: ~85%
  - Low white blood cell count, Neutropenia: ~50%
  - Low platelet count Thrombocytopenia: ~67%

How Do We Diagnose MDS?

Medical History- We ask questions about any health events, health problems, and medications that you have taken in the past and present.

Physical Exam- We examine you from head to toe to identify any symptoms suggesting leukemia

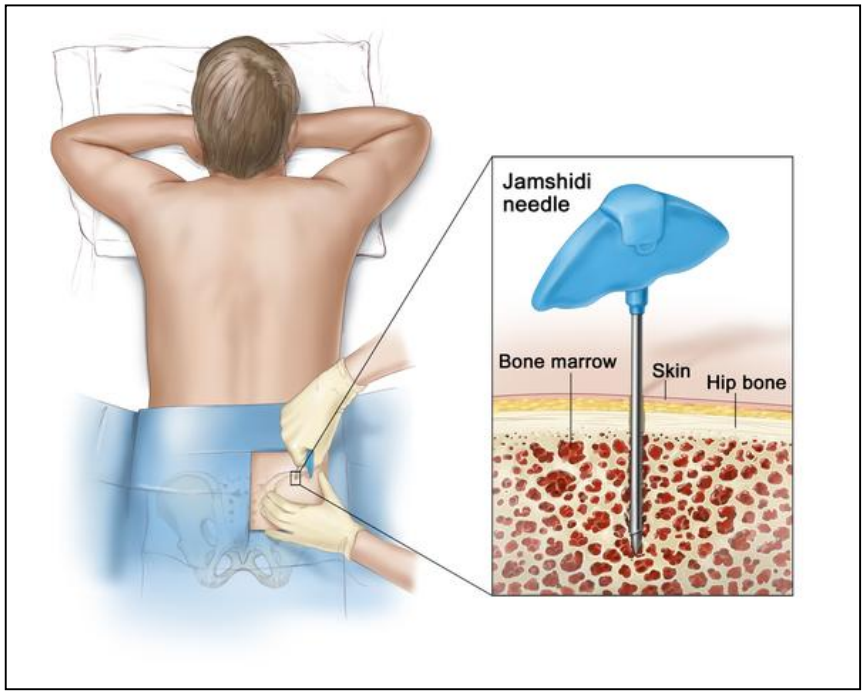
Labs- We take blood work to evaluate your blood counts and complete testing to diagnose leukemia

Bone marrow biopsy and aspirate- Critical to making the diagnosis

Diagnosis

Bone marrow biopsy and aspirate are *essential* to establish the diagnosis, determine the subtype, and determine risk

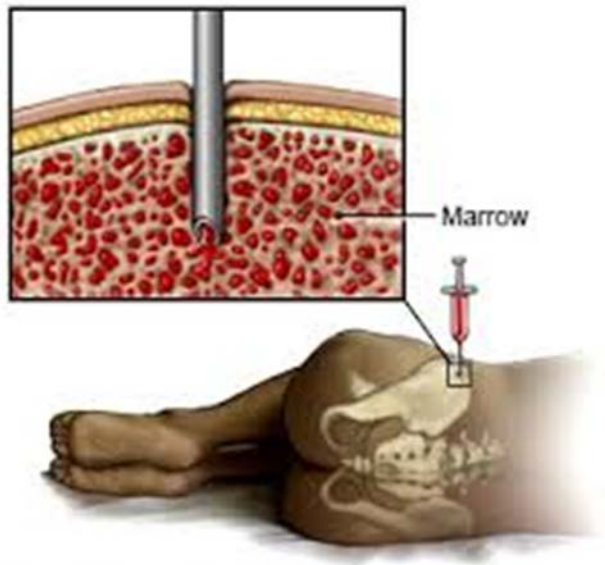
- Morphologic evaluation
- Chromosome analysis (karyotype/cytogenetics)
- Flow cytometry – detect cells with abnormal markers
- Molecular mutations



https://www.healthtap.com/

Bone Marrow Biopsy and Aspirate

Tests from blood or bone marrow
Pathology review of bone marrow to confirm diagnosis
Cytogenetic Testing
Flow cytometry
FISH (Fluorescence in situ hybridization)
PCR (polymerase chain reaction)
Mutation Testing

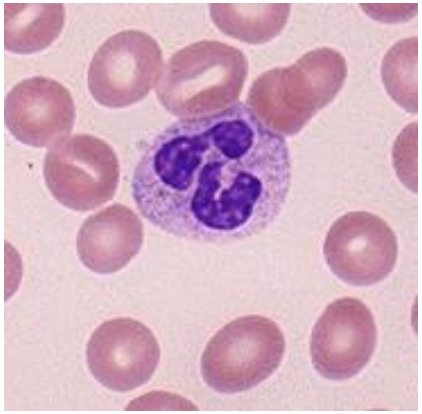


Bone Marrow Aspiration for an Adult

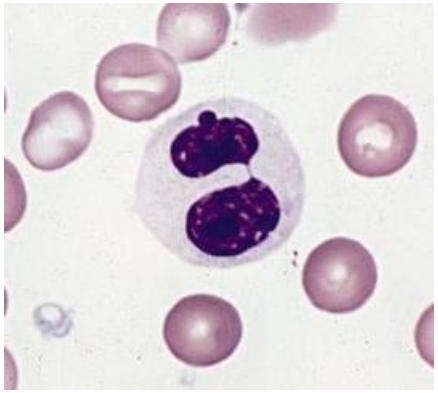
Image from Drugs.com Bone Marrow Biopsy

Blood Cells

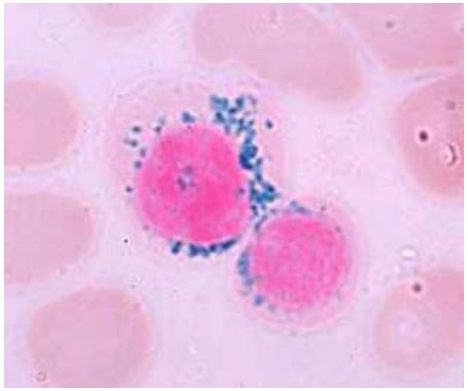
Normal Neutrophil



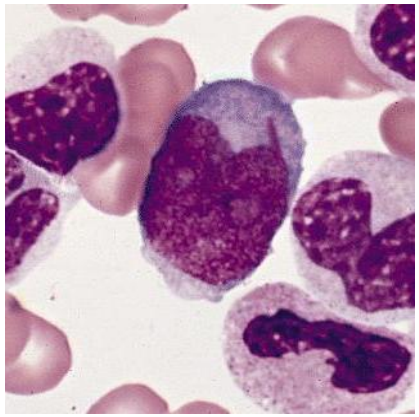
Abnormal/Dysplastic Neutrophil



Ring Sideroblast

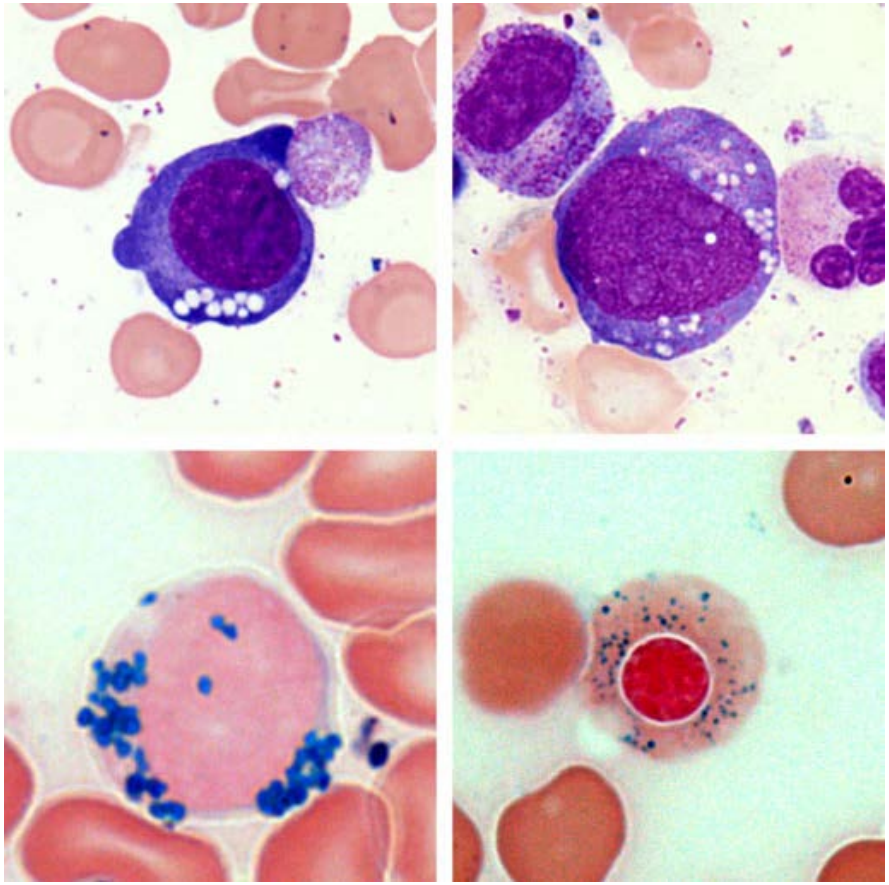


Blast (immature white blood cell)



library.med.utah.edu/WebPath
www.pathologyoutlines.com
www.studyblue.com/notes/note/n/hematology-hp/deck/

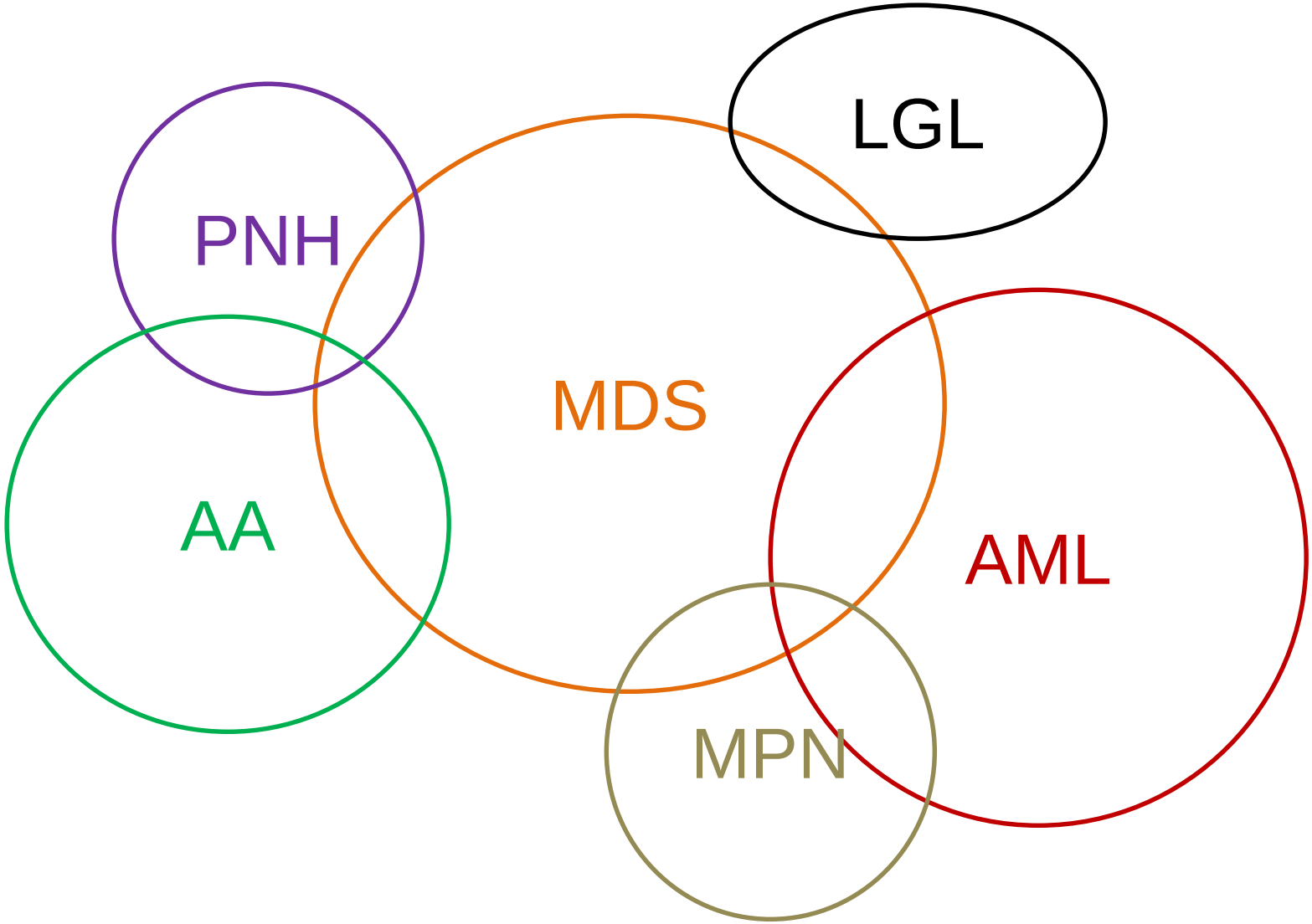
It Is Not Always MDS…



Kobayashi Y. Br J Haematol. 2014 Jan;164(2):161

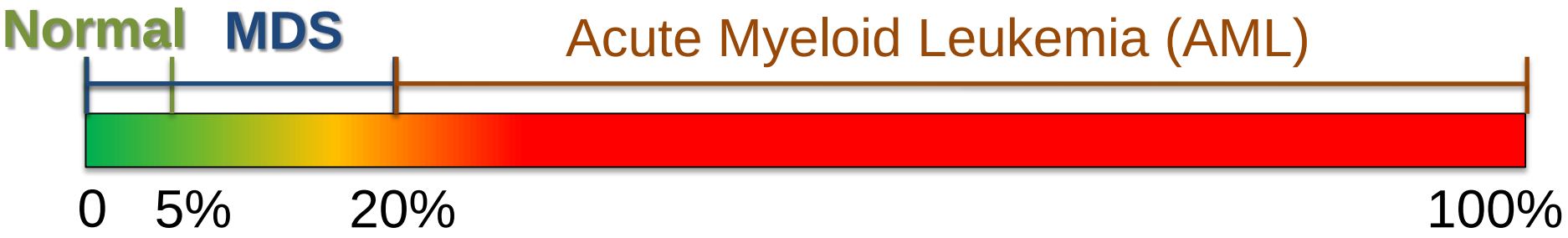
- B12/folate deficiency
- Copper deficiency
- Alcohol
- Medications and Chemotherapy
- HIV, especially while on anti-viral therapy
- Use of growth factors such as G-CSF (Neupogen)

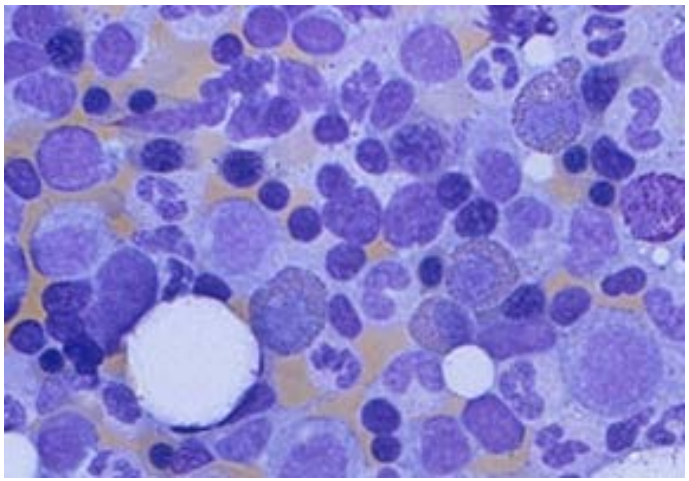
Disease Overlap



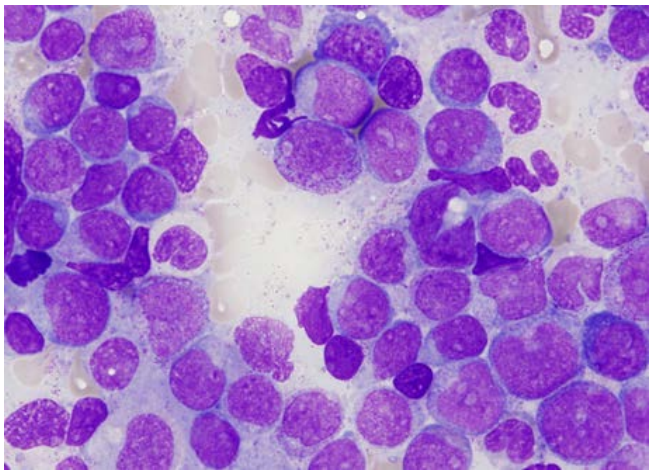
Disease Overlap

Bone Marrow Blasts Percentage





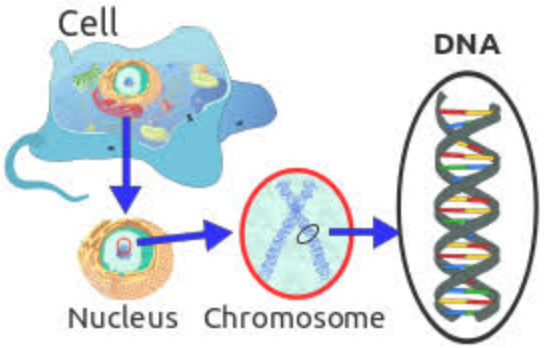
MDS (bone marrow blasts between 5-19%)

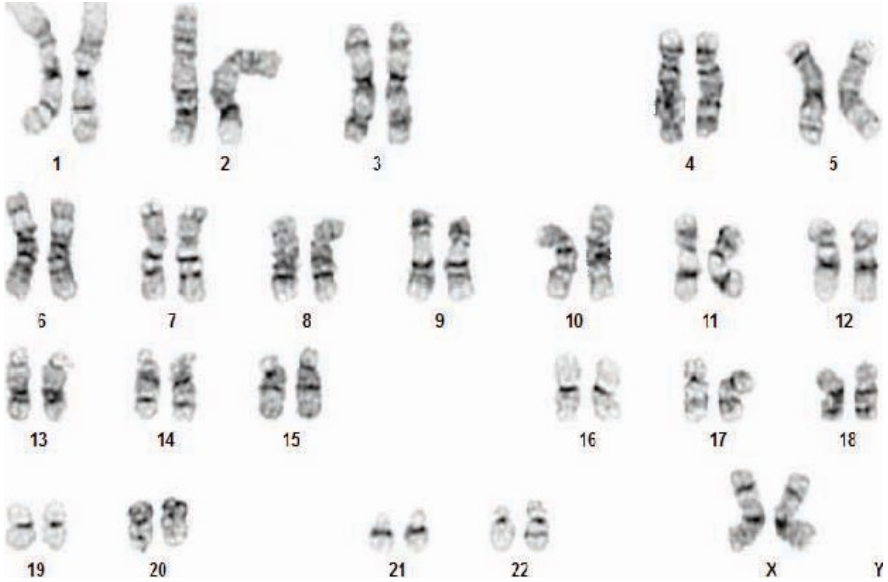


AML (blasts ≥ 20%)

Genetic Tests: Cytogenetic testing

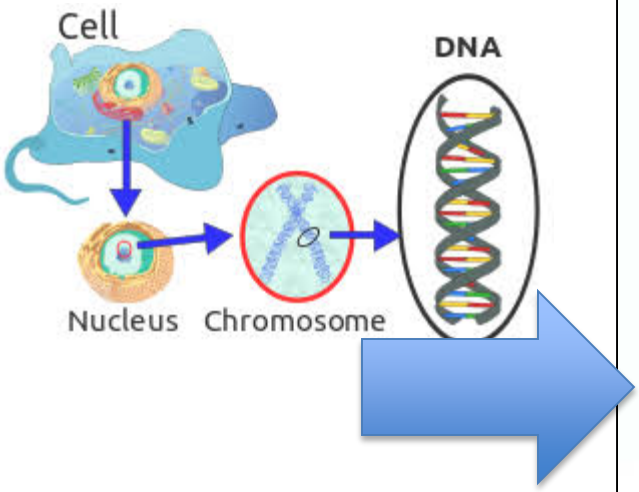
- Cytogenetics uses a microscope to look at the chromosomes inside the leukemia cells to identify the abnormal changes. Completed by a pathologist.
- It is best done from the bone marrow biopsy sample
- Certain chromosome changes in the leukemia cells can affect treatment options including decision on whether a patient needs a bone marrow transplant, what is the best treatment to use, and important for prognosis.
- It can be repeated to evaluate response to treatment (if there is no evidence of the leukemia cells and the chromosome abnormalities are no longer detected, it suggests a great response to treatment)

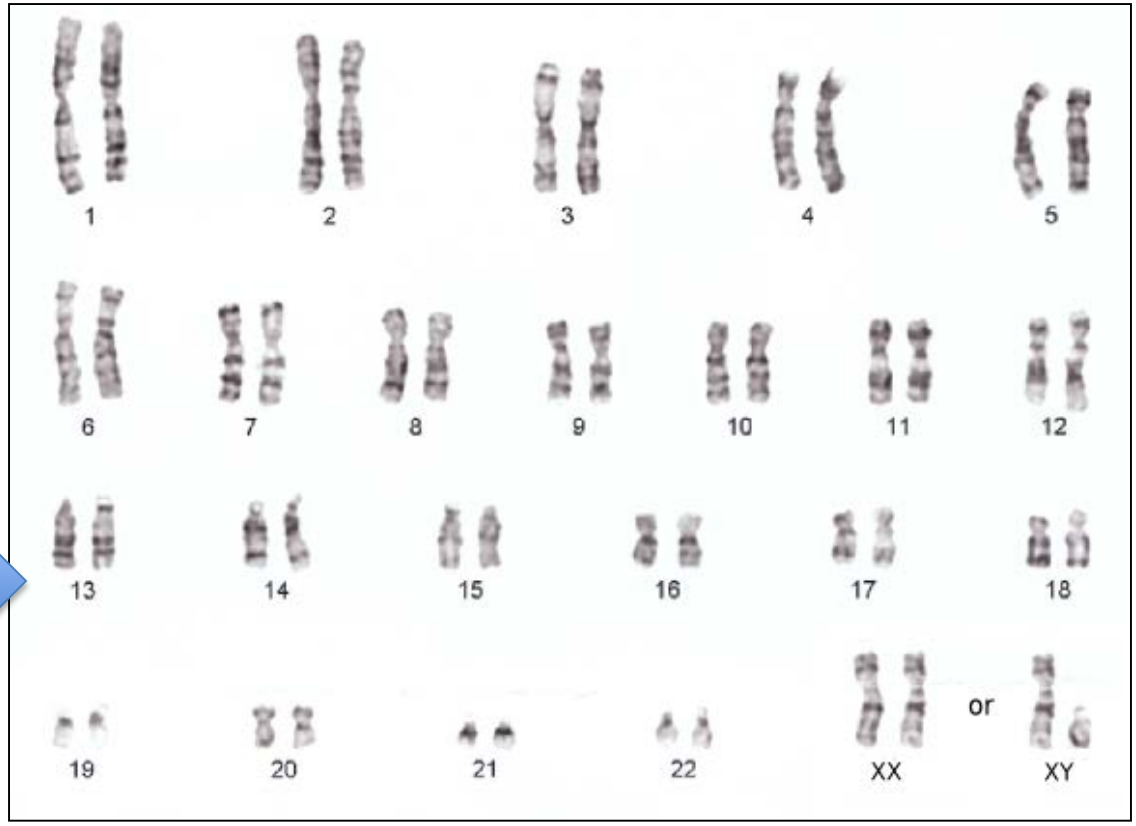




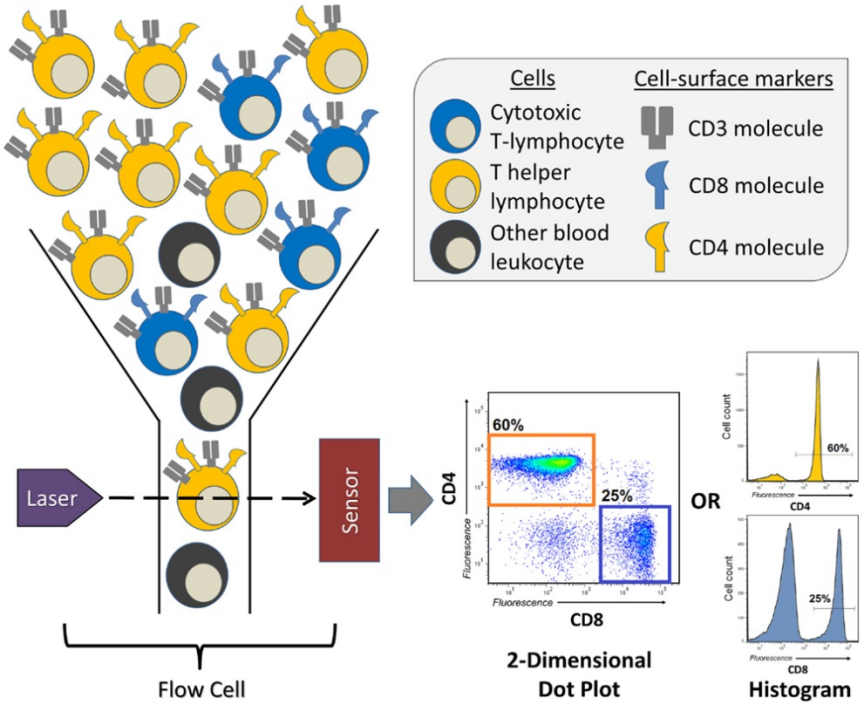
Karyotype/Cytogenetics

- Cells are cultured
- Chromosomes isolated





Flow Cytometry



- Test used to identify and count the different blood cell types in a patient blood sample including percent **blasts**.
- It can help us tell the difference between MDS and other types of leukemia/blood cancers.
- The test helps to confirm the diagnosis of MDS versus AML.
- Flow cytometry can also be used to evaluate whether a patient is responding to treatment.

Image from Frontiers in Immunology
https://www.frontiersin.org/articles/10.3389/fimmu.2015.00380/full

Molecular Studies

- Detects abnormal gene and chromosome changes (mutations) in leukemia cells that are common for AML and ALL.
- These tests are used to decide treatment as well as prognosis
- We now have specific drugs that target certain mutations and chromosome changes that are often oral drugs

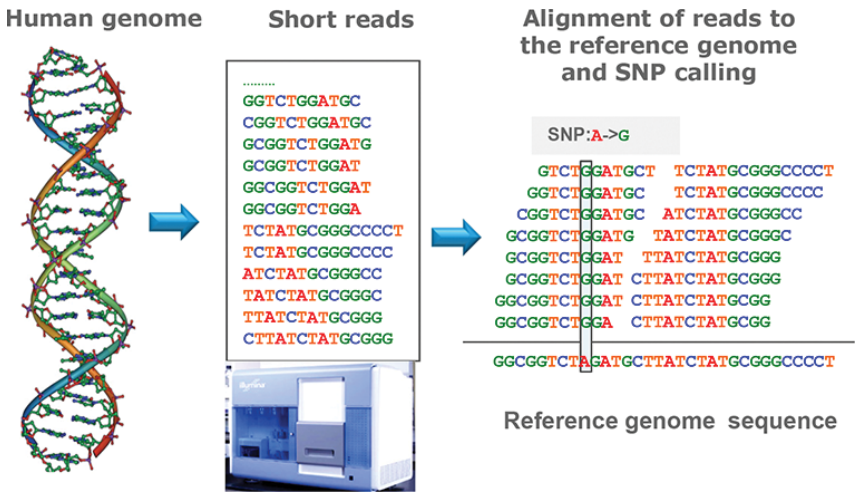


Image Courtesy of Cloud Computing- Architecture and Applications Edited by Jaydip Sen

Additional Testing

- **Echo** of the heart or cardiac nuclear medicine scan: Several drugs have the potential to damage your heart. We check to make sure your heart is beating and pumping normally before giving chemotherapy
- Imaging tests- Rarely and often to evaluate concerning symptoms
  - CT scan, MRI scans, PET scans, ultrasound

Summary of How To Diagnose MDS

- A complete exam with a physician Blood tests are required to help make a diagnosis as well as plan treatment.
- A bone marrow biopsy removes blood from the bone marrow as well as a core bone sample to evaluate your marrow for MDS.
- From the bone marrow bone biopsy and blood sample, very complex and technical tests are completed in order to identify and learn more about the type of MDS you have
- Molecular testing is identifying abnormal genes. Genes tested include TET2, DNMT3A, CEBPA, IDH1, IDH2, TP53, KRAS, and NRAS which helps us classify what type of MDS and answer questions on prognosis.

Test name
Medical History and Physical Exam
CBC with differential (blood counts)
Chemistry panel, LDH, uric acid
Blood clotting tests (PT, PTT, INR)
Fibrinogen
Bone marrow biopsy and aspirate (Key)
Flow Cytometry
Cytogenetics with karyotype and FISH
Molecular testing
HLA typing for bone marrow transplant
Imaging scans
Echocardiogram or MUGA

Chemotherapy

- Drugs used to ***kill cancer*** by killing rapidly growing cells throughout the body including normal and cancer cells
- Different types of drugs work in multiple different ways. We have learned that specific combinations of different drugs can actually improve the overall function of each drug. Combining separate drugs together is called **multi-agent chemotherapy**
- Given in ***cycles*** of treatment days followed by days of rest **allowing the body to recover before the next treatment**.
  - Example is drug given days 1 through 7 in a 28 day cycle (averages out to be about every 7 days in a month)
  - We monitor how many cycles of treatment you have received

Chemotherapy Delivery

A. Peripheral IV access in the hand
B. Peripheral IV catheter at the elbow
C. Midline catheter
D. Central Venous Catheter
E. Tunneled Central Venous Cather- more permanent
F. Port (implanted under the skin)
G. PICC line (Peripherally inserted central catheter)

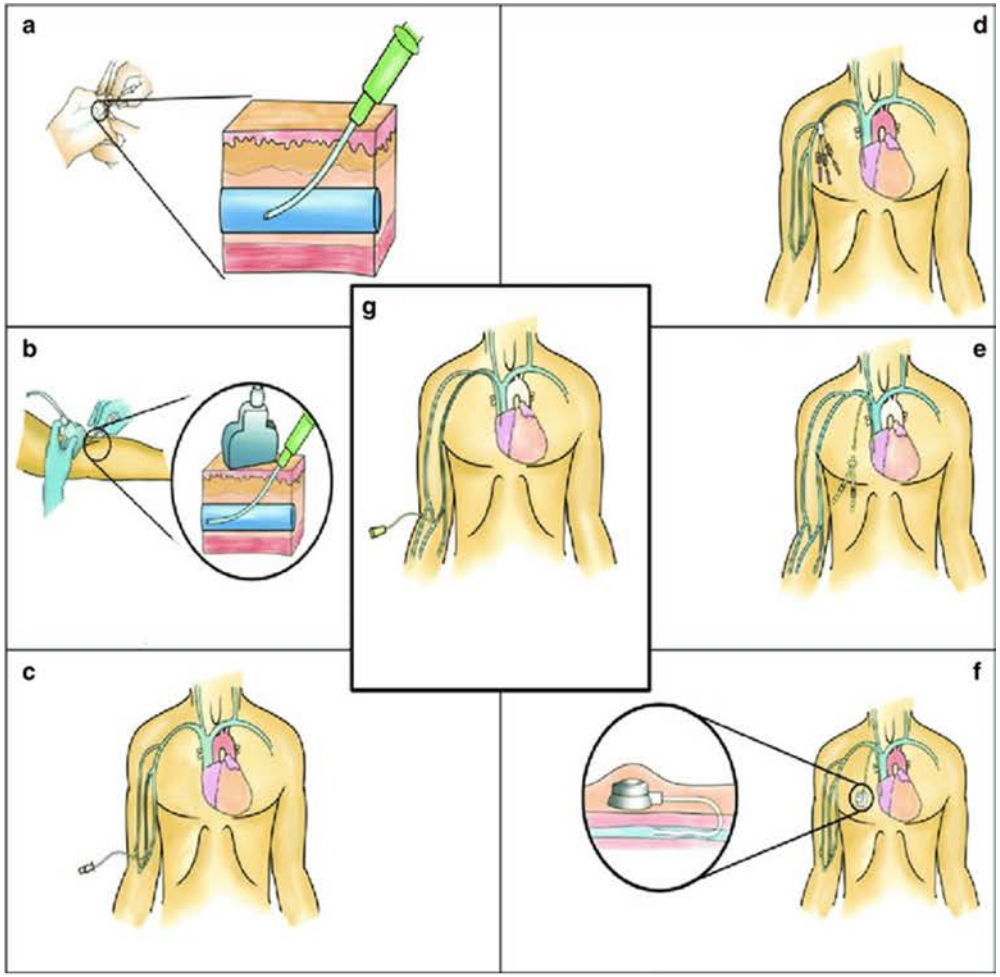
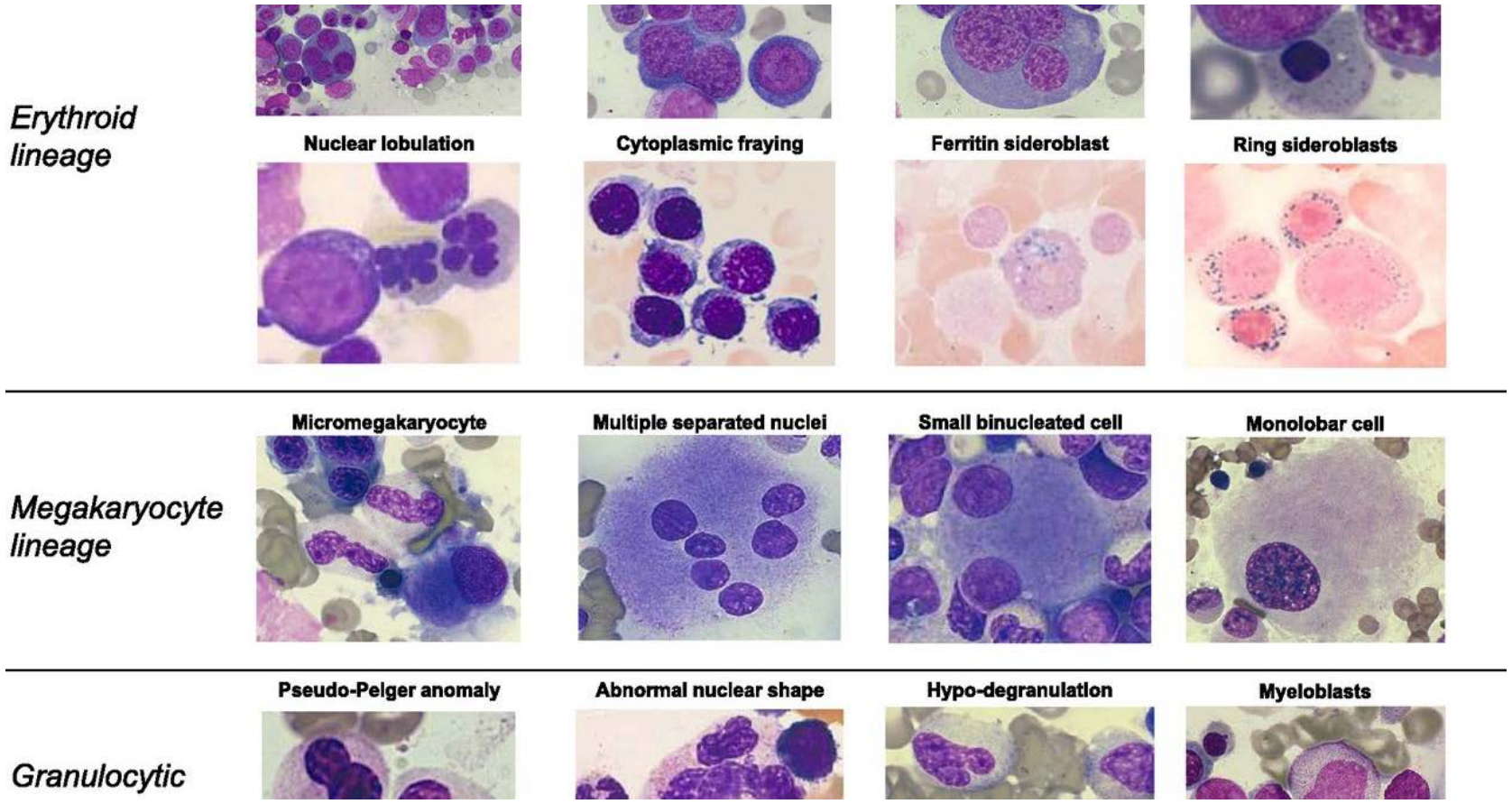


Image Courtesy of The Conversations https://theconversation.com/is-your-doctor-choosing-the-right-iv-48199

It is MDS, What Do We Do Now?



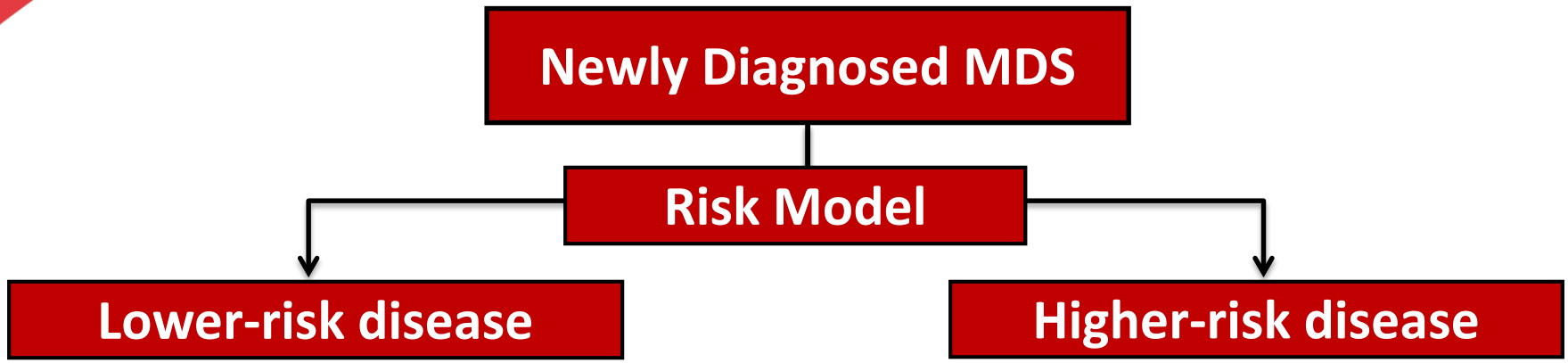
Cazzola, M et al. The genetic basis of myelodysplasia and its clinical relevance. Blood. 2013. 122:4021-4034

2016 WHO Classification

Classification	Dysplastic Lineages	Cytopenias	Ring Sideroblasts	BM and PB Blasts	Karyotype
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%*	BM<5%, PB<1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS) MDS-RS with single lineage dysplasia (MDS-RS-SLD) MDS-RS with multilineage dysplasia (MDS-RS-MLD)	1 2 or 3	1 or 2 1-3	≥15%/≥5%*	BM<5%, PB<1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM<5%, PB<1%, no Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del (7q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%*	BM<5%, PB<1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with excess blasts (MDS-EB) MDS-EB-1 MDS-EB-2	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U) With 1% blood blasts	1-3	1-3	None or any	BM<5%, PB=1%, no Auer rods	Any
With single lineage dysplasia and pancytopenia	1	3	None or any	BM<5%, PB<1%, no Auer rods	Any
Based on defining cytogenetic abnormality	0	1-3	<15%	BM<5%, PB<1%, no Auer rods	MDS-defining abnormality

*If SF3B1 mutation is present.

Risk Assessment



Treatment Goal:

- Decrease the number of blood transfusions to less often or none at all
- Improve symptoms
- Improve quality of life

Treatment Goal:

- Alter natural history of disease
- Prevent progression to AML
- Improve overall survival

International Prognostic Scoring System

	0	0.5	1.0	1.5	2
BM blasts (%)	<5	5-10	--	11-20	21-30
Karyotype*/ Cytogenetics	Good	Intermediate	Poor		
Cytopenias (number abnormal blood counts)	0/1	2/3			

*Good Karyotype/Cytogenetics: normal, -y, del(5q), del(20q)

*Poor Karyotype/Cytogenetics: complex (more than 3 abnormalities) or chromosome 7 is abnormal

*Intermediate: all others Karyotype/cytogenetic abnormalities

	Median Survival (yrs)
Low (0)	5.7
Int-1 (0.5-1)	3.5
Int-2 (1.5-2)	1.2
High (≥ 2.5)	0.4

Greenberg P et al, Blood 1997; 89:2079-88

Revised IPSS

Prognostic Subgroup	Cytogenetic Abnormality	Median Survival, y
Very Good	-Y, del(11q)	5.4
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones	2.7
Poor	-7, inv(3)/t(3q)/del(3q), double including-7/ del(7q), complex: 3 abnormalities	1.5
Very Poor	Complex: > 3 abnormalities	0.7

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	--	Good	--	Int	Poor	Very Poor
BM blast, %	≤ 2	--	>2 - <5	--	5 - 10	>10	--
Hemoglobin, g/dL	≥ 10	--	8 - <10	< 8	--	--	--
Platelets, K/μL	≥ 100	50 - <100	< 50	--	--	--	--
ANC, K/μL	≥ 0.8	< 0.8	--	--	--	--	--

Greenberg P. Blood 2012;120: 2454-2465

Revised IPSS

Category	Score
Very Low	≤ 1.5
Low	> 1.5 – 3
Intermediate	> 3 – 4.5
High	> 4.5 – 6
Very High	> 6

Less Aggressive Disease

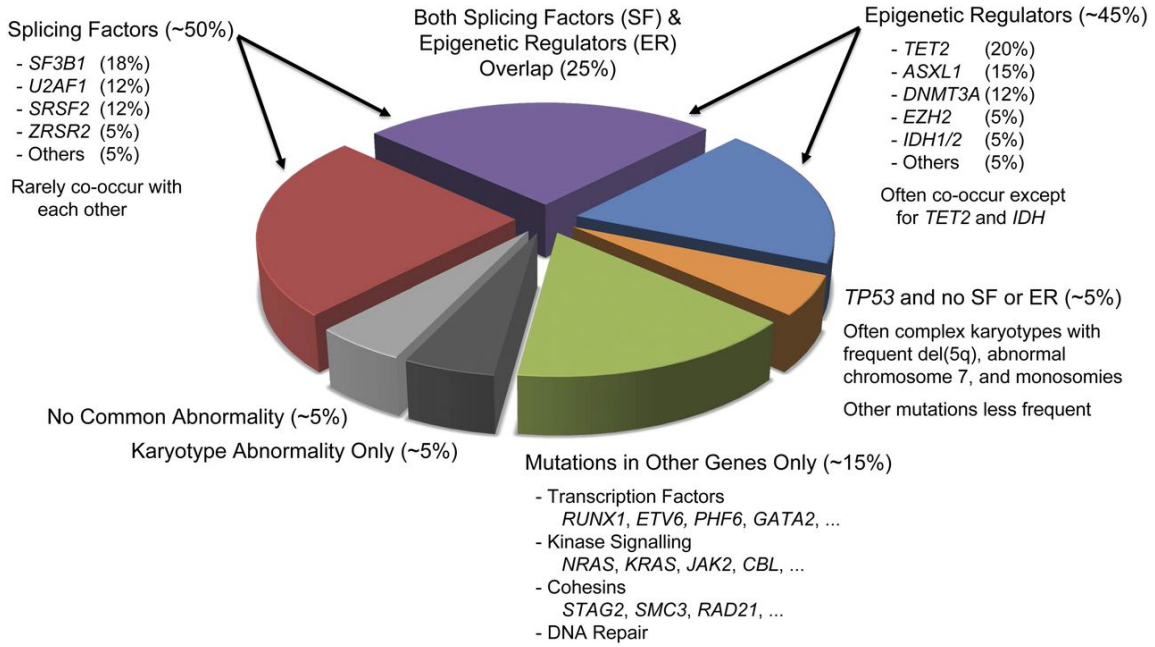
Very Aggressive Disease

	Survival, y	HR for OS
Very low	8.8	0.5
Low	5.3	1.0
Intermediate	3.0	2.0
High	1.6	3.2
Very High	0.8	8.0

Greenberg P. Blood 2012;120: 2454-2465

Molecular Mutations in MDS

- >90% of patients with MDS have at least 1 mutation or abnormal gene



- Some mutations are associated with more aggressive disease: TP53, RUNX1, ASXL1, etc.

Bejar R and Steensma D, Blood 2014

Standard Treatment Options

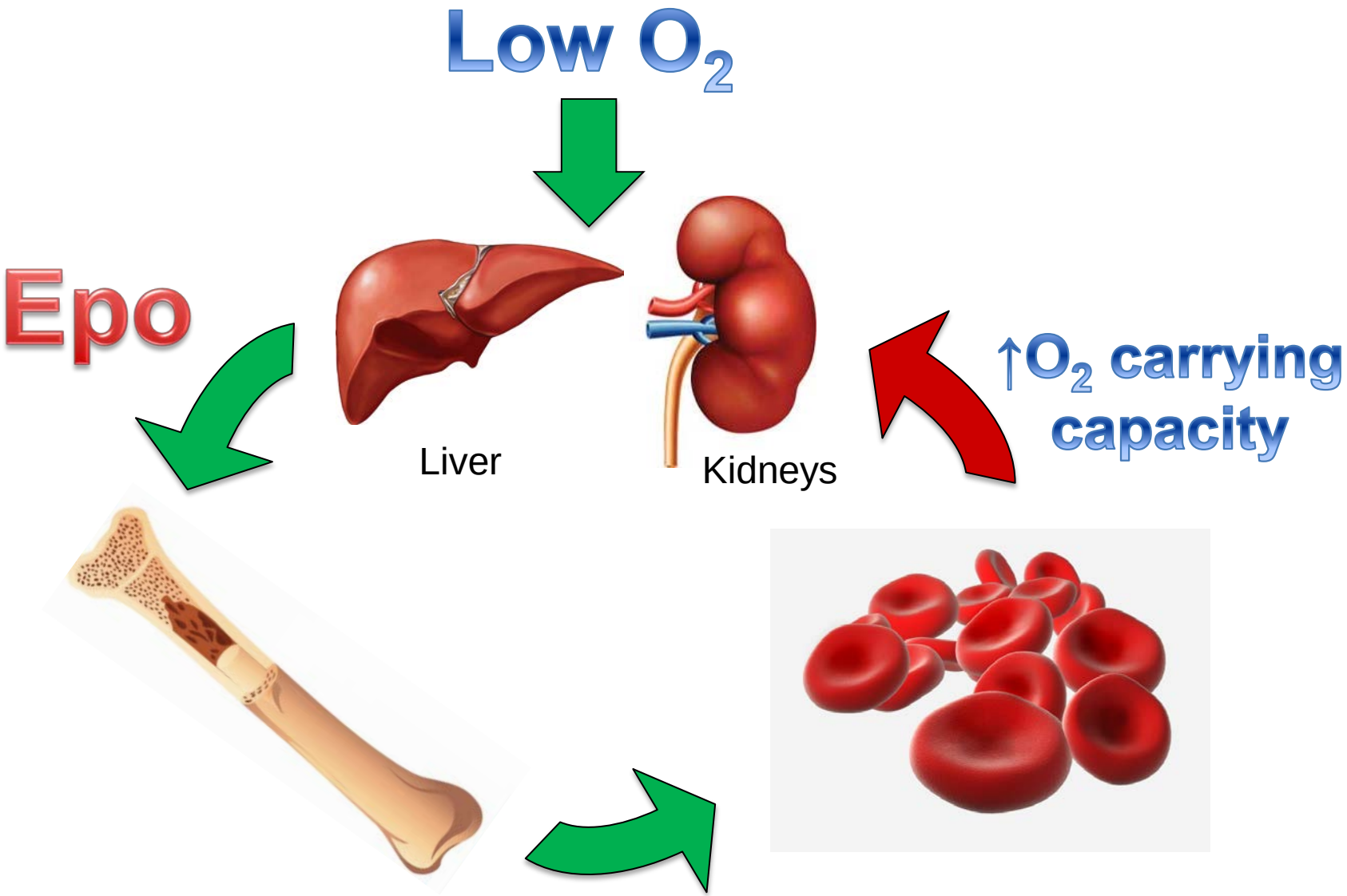
- Lower Risk Disease
  - Observation
  - Growth Factors
  - Immunosuppressive Therapy
  - Lenalidomide
  - Hypomethylating Agents
- Higher Risk Disease
  - Hypomethylating Agents: **Azacitidine** (Vidaza®) and **Decitabine** (Dacogen®)
  - Intensive Chemotherapy
- Bone Marrow Transplantation

Lower-risk Disease: Current Standard of Care

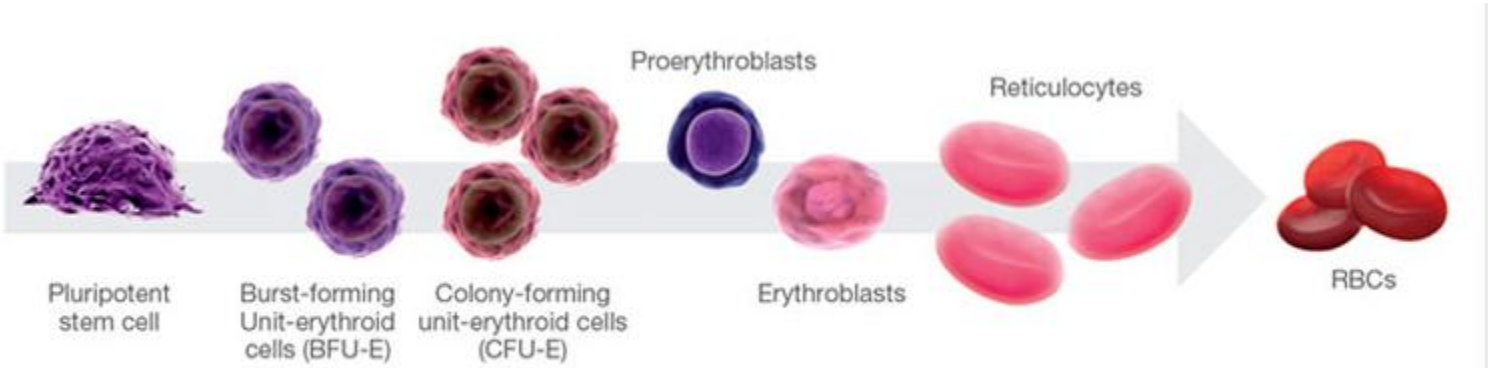
Observation

- Not all patients need active therapy for MDS
  - Mild peripheral blood abnormalities
  - Patient does not require blood transfusions
  - No or few symptoms
- Treating lower-risk patients early has *NOT* been shown to improve outcomes

Erythropoetin



Erythropoiesis Stimulating Agents



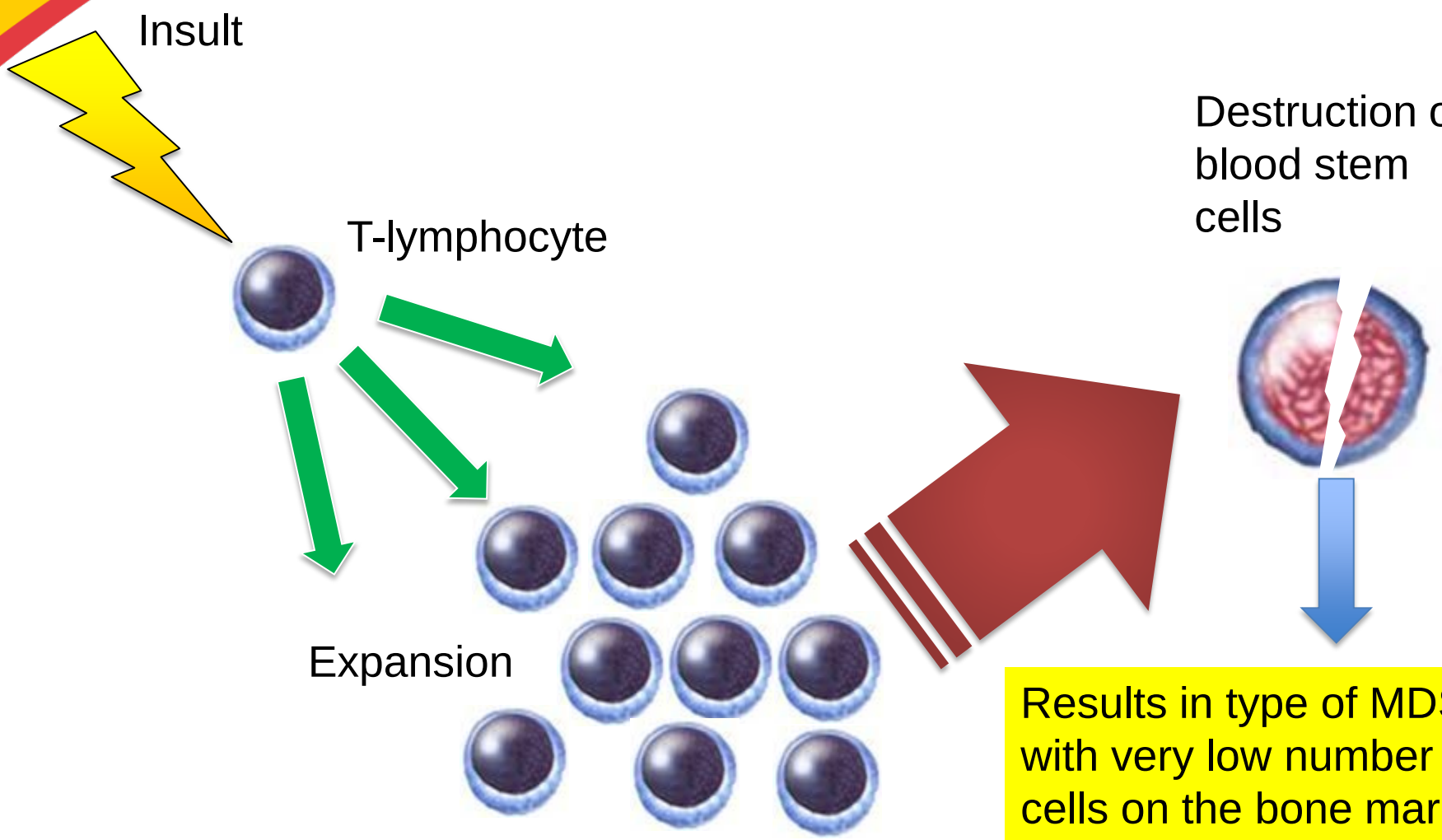
- Injections to stimulate bone marrow to make more red blood cells
- Not all patients respond to these medications: 30-40% response rates
- Epoetin alfa and darbepoetin are likely as effective
- Addition of G-CSF (growth factors) may be helpful

Caution with ESAs

- Linked to increased heart attacks, stroke, blood clots, tumor growth, and death in patient with solid tumors

- This HAS NOT been shown in patients with MDS

Immune-Mediated Destruction



Results in type of MDS with very low number of cells on the bone marrow biopsy

Anti-Thymocyte Globulin & Cyclosporine

- Kill and block activity of T cells, restoring blood production
- Response rate ~30%
- Possible side effects: Allergic reactions, serum sickness, increased risk of infections, kidney dysfunction, neurologic issues

Passweg JR, JCO 2010

Anti-Thymocyte Globulin & Cyclosporine

Favorable factors for response to Immunosuppressive Therapy:

- Young Age
- Immune receptor type (HLA-DR15)
- Low cellular marrow/Hypocellular marrow
- PNH clones
- Ratio of T-cell subtypes (Low CD4:CD8)

2016 WHO Classification

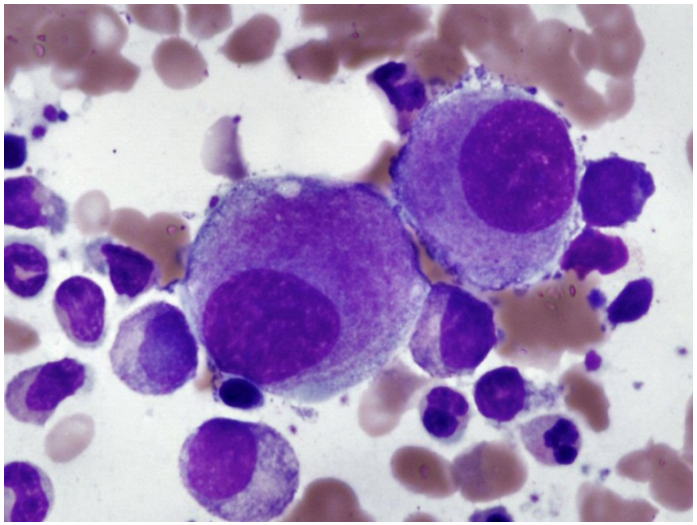
Classification	Dysplastic Lineages	Cytopenias	Ring Sideroblasts	BM and PB Blasts	Karyotype
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%*	BM<5%, PB<1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS) MDS-RS with single lineage dysplasia (MDS-RS-SLD) MDS-RS with multilineage dysplasia (MDS-RS-MLD)	1 2 or 3	1 or 2 1-3	≥15%/≥5%*	BM<5%, PB<1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM<5%, PB<1%, no Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del (7q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%*	BM<5%, PB<1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with excess blasts (MDS-EB) MDS-EB-1 MDS-EB-2	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U) With 1% blood blasts	1-3	1-3	None or any	BM<5%, PB=1%, no Auer rods	Any
With single lineage dysplasia and pancytopenia	1	3	None or any	BM<5%, PB<1%, no Auer rods	Any
Based on defining cytogenetic abnormality	0	1-3	<15%	BM<5%, PB<1%, no Auer rods	MDS-defining abnormality

*If SF3B1 mutation is present.

MDS with isolated del(5q)

- Specific Type of MDS
- 10-15% of patients with MDS

- Presentation:
  - No increased blasts on marrow
  - Isolated anemia (low hemoglobin)



- Female predominance

- Low risk of progression

MDS Treatment for isolated del(5q): Lenalidomide

- Oral chemotherapy capsule taken daily
- Improves anemia in patients with lower-risk disease and del(5q)

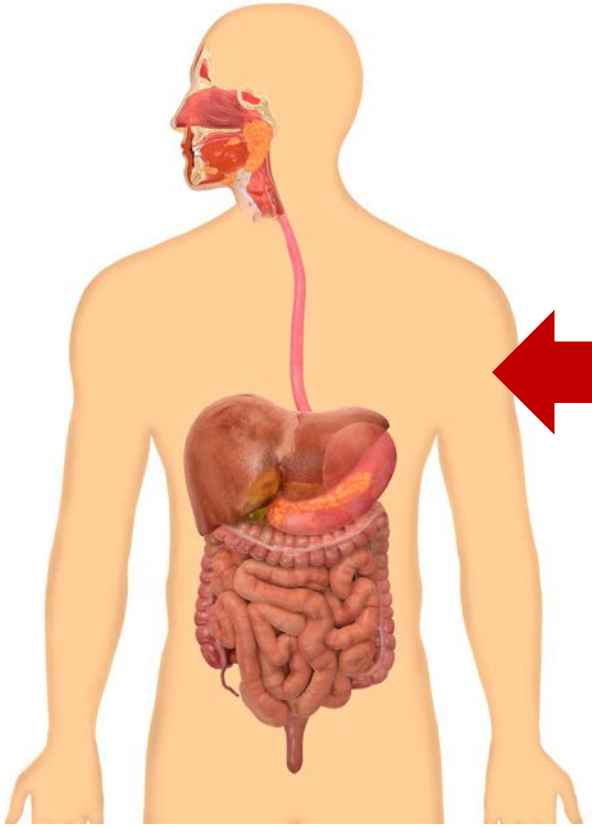
	All patients (n=148)
Erythroid Response	
Transfusion Independence	**67%**
≥50% decrease in transfusions	**9%**
Total Transfusion Response	**76%**
Median Time to Response (weeks)	**4.6**

- Often causes decreased neutrophils (low white blood cell count) and platelets

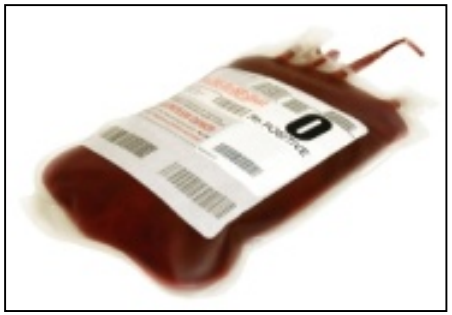
List AF, N Engl J Med 2006;355:1456-65

Iron Balance in Patients Requiring Blood Transfusions Chronically

Daily intake: 1-2 mg



Daily losses: 1-2 mg



~250 mg/unit

Long-term complications from high iron levels in the body:

- Heart failure
- Liver disease
- Diabetes
- Skin changes
- Endocrine dysfunction

Treatment for high iron levels from blood transfusions: Iron Chelation Therapy

- Deferasirox decreases serum ferritin but high discontinuation rates

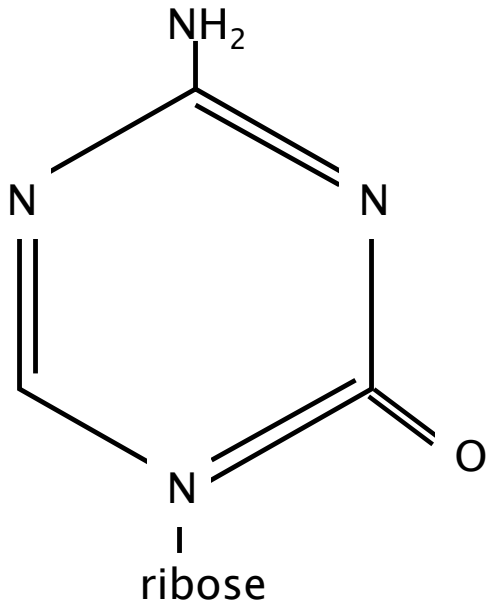
- Consider:
  - Lower-risk MDS disease with long life expectancy
  - Serum ferritin on blood work greater than 1,000-2,500 mcg/L or other clinical evidence of iron overload

Higher-risk Disease: Current Standard of Care

Hypomethylating Agents

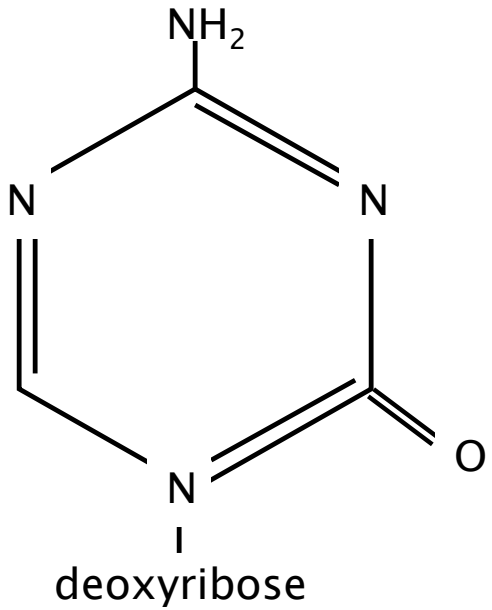
5-Azacitidine

(Vidaza®)



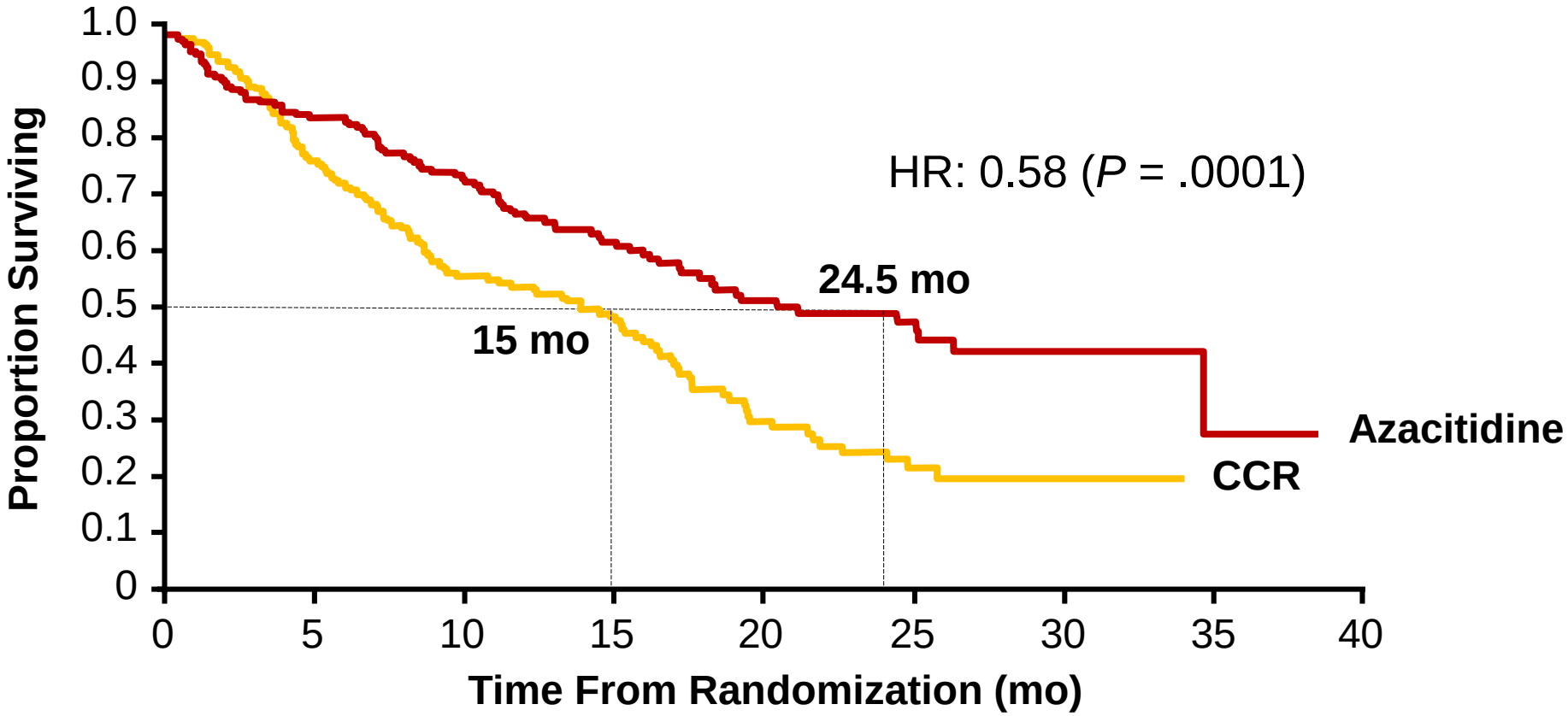
Decitabine

(Dacogen®)



AZA-001: Azacitidine vs. CCR

Overall patients with MDS had better outcomes with Azacitidine (Vidaza®)



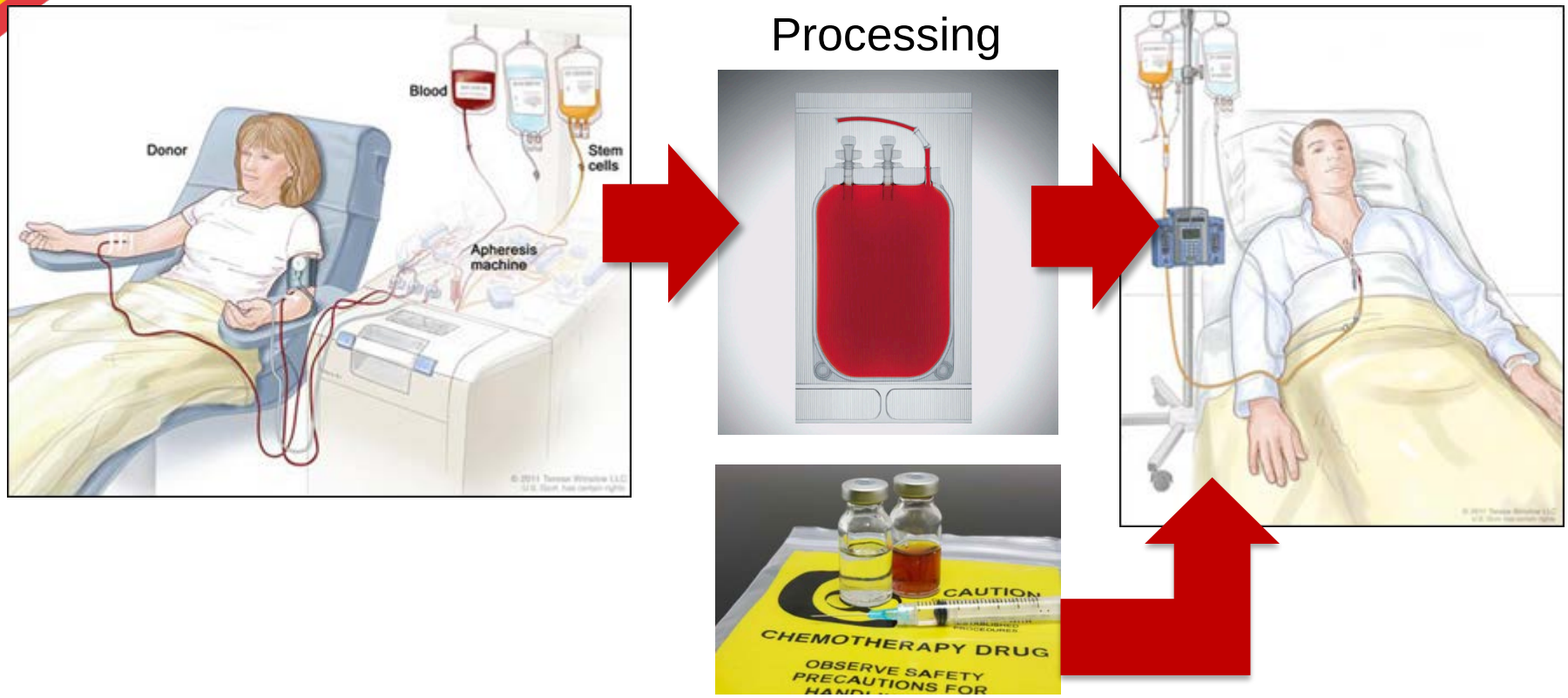
Fenaux P, et al. Lancet Onc 2009;10:223

Hypomethylating Agents: Other Issues

- Typical number of cycles required to 1st response: 2-3 cycles/months of treatment[1,2]
- Patients who respond must continue treatment indefinitely
- Do NOT need a complete response to benefit[3]
- Side effects: Decreased blood counts, nausea, constipation, fatigue, *infections which can be life threatening*
  - Side effects usually manageable without discontinuation of drug

1. Silverman LR, JCO 2006
2. Silverman LR, Cancer 2011
3. List AF, ASCO 2008, Abstract #7006

Bone Marrow or Stem Cell Transplantation

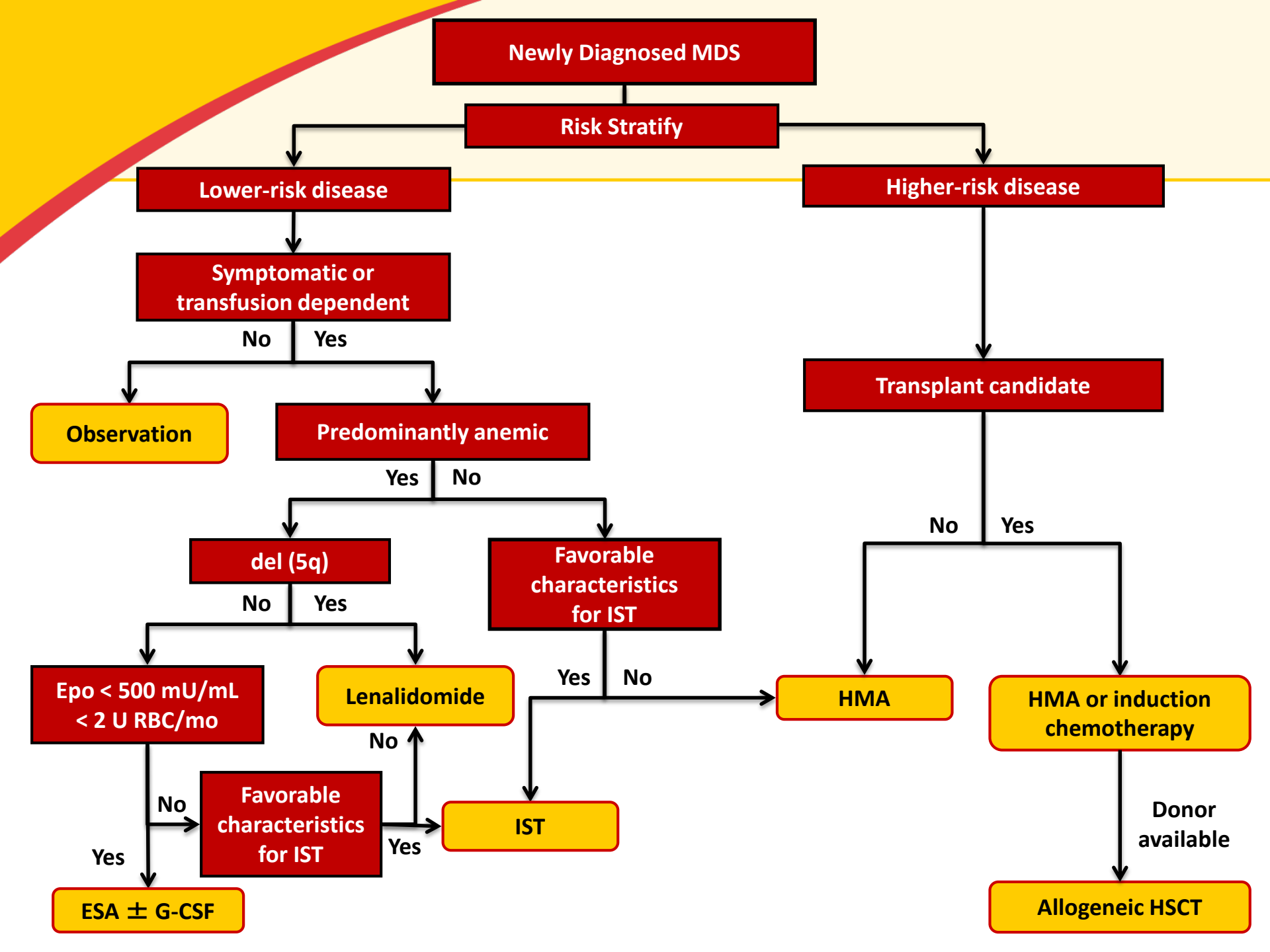


- The ONLY potential cure for MDS
- Very intensive, toxic therapy

https://www.cancer.gov/publications/dictionaries/

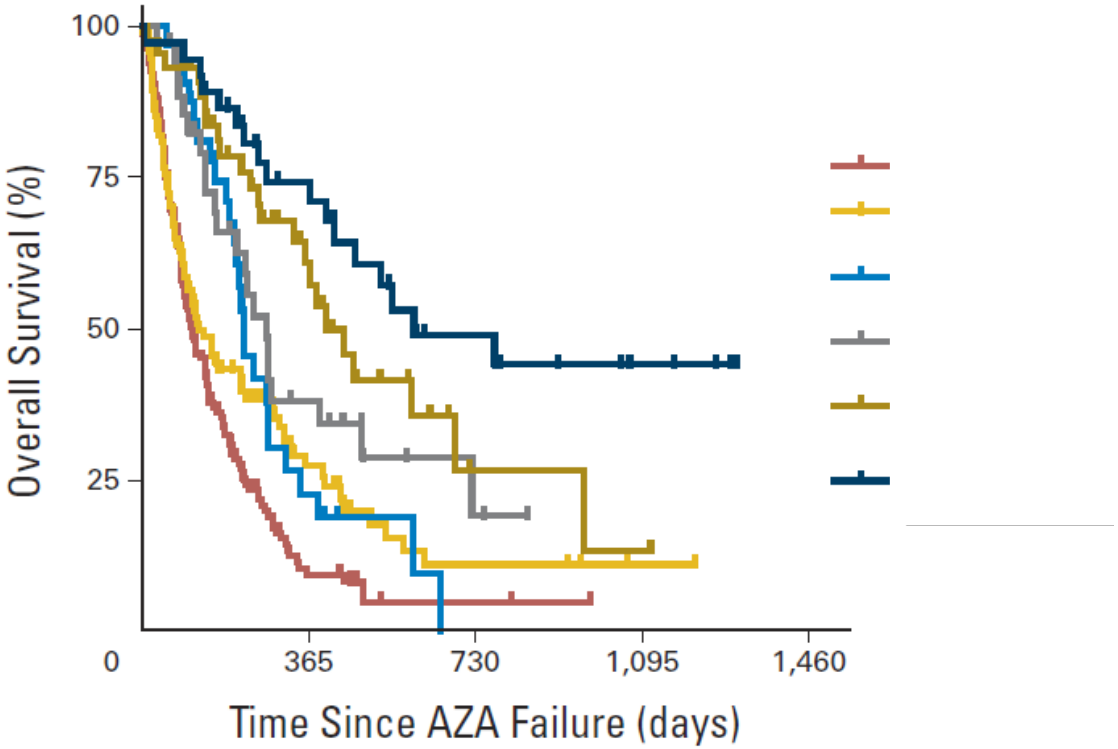
Bone Marrow Transplantation

- Graft Versus Host Disease
  - Skin
  - GI tract
  - Liver
  - Others
- Liver Toxicity and Damage
  - Painful/enlarged liver, weight gain, fluid retention, yellow color (jaundice)
  - Can lead to liver failure
- Mucositis (mouth sores, pain with swallowing)
- Infections which can be life threatening


Newly Diagnosed MDS
Risk Stratify
Lower-risk disease
Higher-risk disease
Symptomatic or transfusion dependent
No
Yes
Observation
Predominantly anemic
Yes
No
del (5q)
No
Yes
Epo < 500 mU/mL < 2 U RBC/mo
Lenalidomide
No
Yes
ESA ± G-CSF
Favorable characteristics for IST
No
Yes
Favorable characteristics for IST
Yes
No
IST
HMA
Transplant candidate
No
Yes
HMA or induction chemotherapy
Donor available
Allogeneic HSCT

What to do after Vidaza and/or Dacogen?

- Unfortunately we do not have great treatment options after Azacitidine (Vidaza) or Decitabine (Dacogen) stop working
- No standard of care



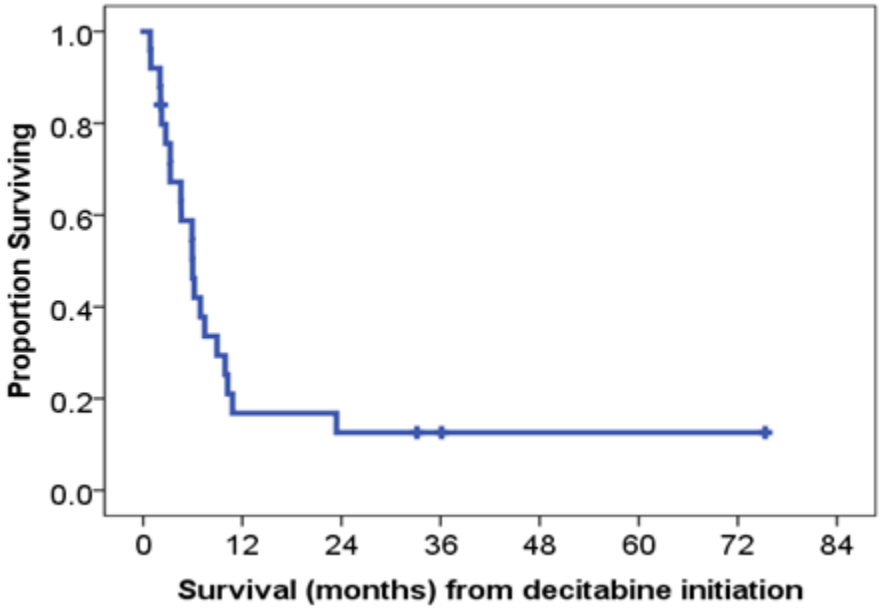
Prébet T et al, JCO 2011; 29:3322

Decitabine after Azacitidine

- MDACC prospective clinical trial result:
  - 28% Response Rate (3/14)

Borthakur G, Leuk Lymphoma 2008

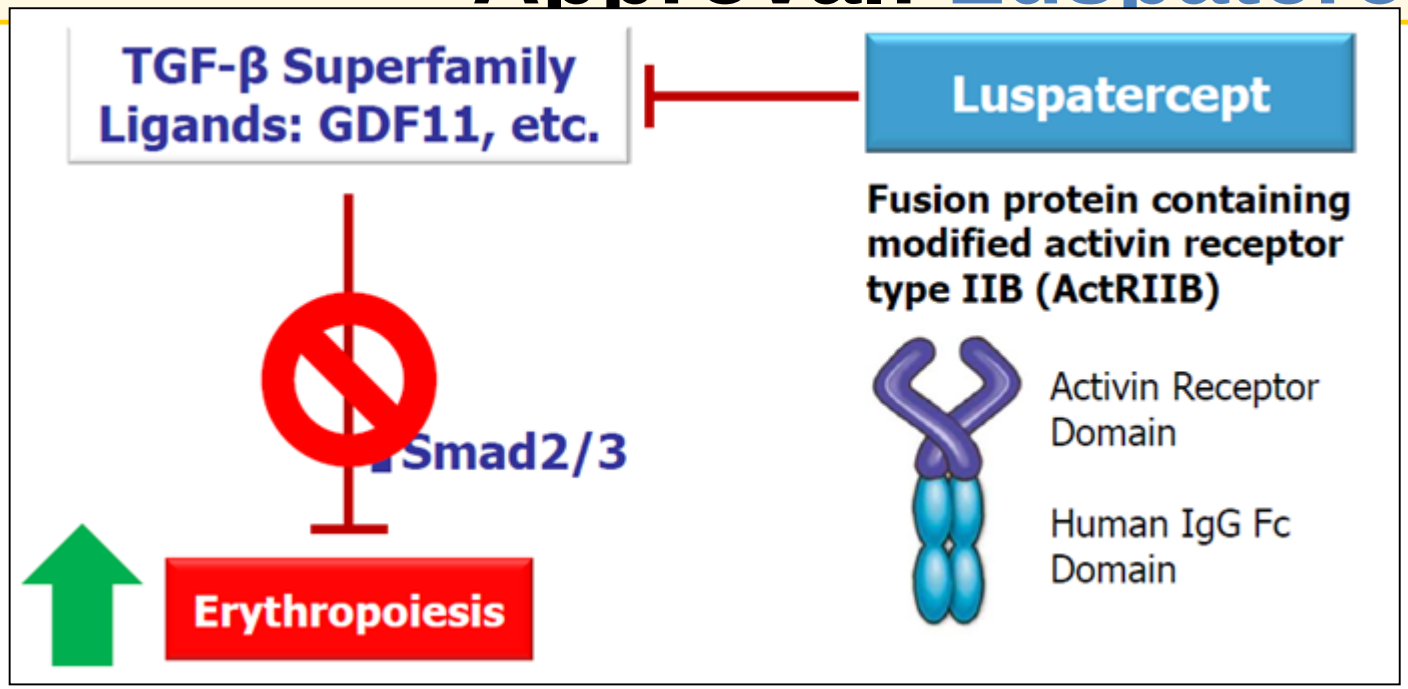
- Univ. of Maryland experience:
  - No clear responses in 25 patients with MDS or AML

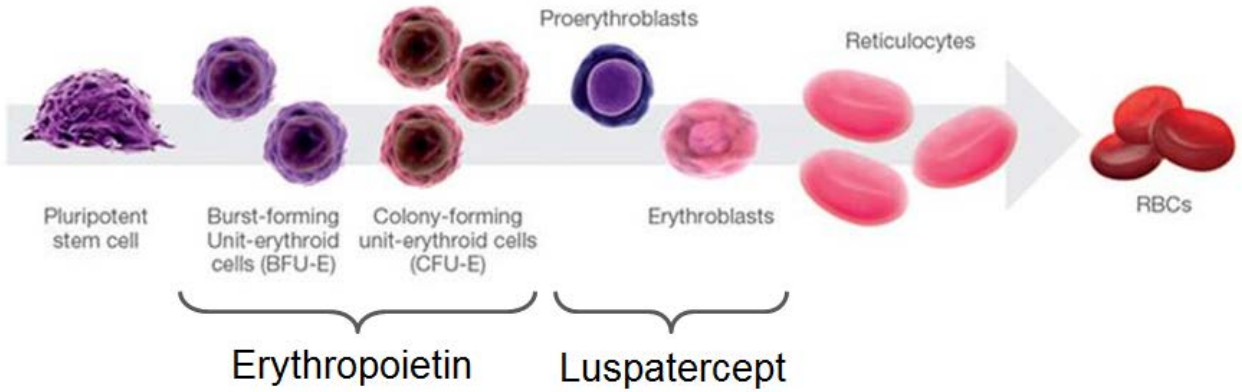


Duong VH, Leuk Lymphoma 2014

Advancements in Lower-Risk Disease

Recently Submitted for FDA Approval: Luspatercept





http://www.acceleronpharma.com/wp-content/uploads/2014/12/ASH-536-MDS-Oral-Presentation-FINAL.pdf

Advancements in Higher-risk Disease

Venetoclax– BCL-2 Inhibitor

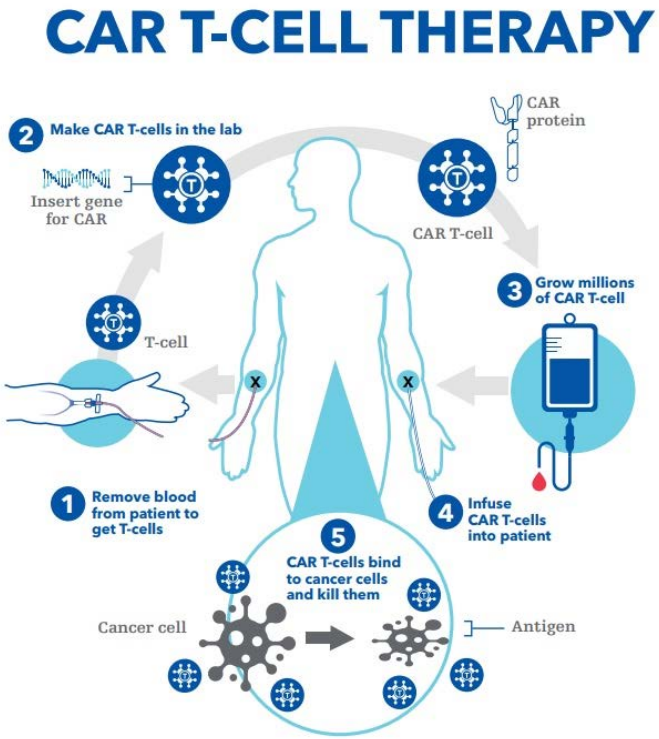
- Phase II Trial
  - Venetoclax is an oral medication used in combination with either Decitabine or Azacitidine
  - Clinical trials are ongoing across the country including at University of Maryland

Image from www.venclexta.com Abbvie

CAR T-cell Therapy

CAR-T cell therapy is type of treatment where a patient's T-cells are genetically altered in the laboratory so that they will bind to specific proteins (antigens) ono cancer cells and kill them.

1) T-cells are removed from the patient's blood
2) Gene for a specific receptor alled chimeric antigen receptor (CAR) is inserted into the T-cells in the laboratory. The gene has instructions to produce on the surface of the patient's T-cells creating the CAR T-cell
3) Millions of CAR T-cells are grown in the laboratory
4) They are then given to the patients by IV infusion
5) The CAR T-cells bind to antigens on the cancer cells and kill them

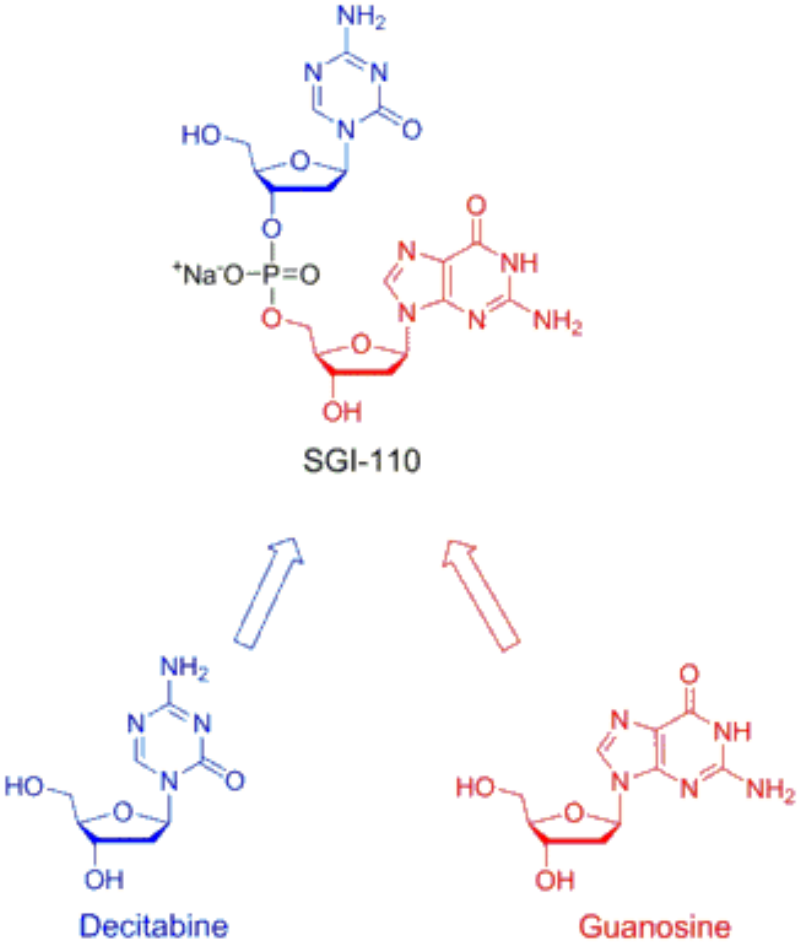


Courtesy of UK HealthCare

Azacitidine Combination Studies

Drug	Target	Identifier
Durvalumab (MEDI4736)	PD-L1	NCT02775903
Nivolumab	PD-1	NCT02530463
Ibrutinib	BTK	NCT02553941
Vosaroxin	Topoisomerase II	NCT01913951
Pevonedistat	NEDD8	NCT02610777
Venetoclax	BCL-2 Inhibitor	
Eltrombopag	TPO-R	NCT02158936
PF-04449913 (Glasdegib)	Hedgehog Pathway	NCT02367456
Vadastuximab Talirine (SGN-CD33A)	CD33	NCT02706899
Rigosertib	PLK-1	NCT01926587
Sirolimus	mTOR	NCT01869114

SGI-110 (Guadecitabine)



- Similar to decitabine and azacitidine
- Stays active in your body for longer period of time
- Longer exposure time

Supportive Care While Receiving Treatment

Supportive Care	Trying to improve your quality of life while receiving treatment
Abnormal blood cell counts - Giving blood transfusions	Due to MDS and chemotherapy, your red blood cells (**hemoglobin**) and **platelets** can be low. You **may require transfusions** to make you feel better (improve fatigue/tiredness) and decrease chances of dangerous bleeding from low platelets
Infections - Starting anti-viral, antibiotic, and anti-fungal treatment	You are at risk for infections (from viruses, fungus, or bacteria) especially when your **white blood cell counts** are low. We start medications to prevent and treatment infections which can be fatal if not treated early
Depression/Anxiety	Please let your doctor know if you are feeling overwhelmed or need more support/help
Nausea/Vomiting/Diarrhea/Constipation	We have very effective treatment to prevent and treat nausea/vomiting
Cancer-related pain	Make sure to notify your doctor regarding any pain or discomfort outside of the norm

Making Treatment Decisions

- This is a Team Sport. Treatment decisions are made with you, your family, and your physician all working together.
- Bring a Buddy to doctor visits
  - Consider designating a medical Power of Attorney before starting treatment

- ❖ Please ask questions!
- Compare benefits and downsides of each treatment option
- Do not be afraid to say “No” or “Stop”
- Do careful research:

  NCCN Guidelines for patients at http://www.nccn.org and choose Patient Resources and then NCCN Guidelines for Patients

Image Courtesy
brucedwatson.wordpress.com

Please Ask Questions!

- Bring a Buddy to doctor visits
- Take Notes
- Ask for copies of labs and important test results including your bone marrow biopsy reports, cytogenetic results, and molecular results
- ***Ask questions…Always ask questions***
- Know what medications you are taking and will take in the future
  - **Bring a list**
- Ask your doctor to write out a treatment plan and make sure to update your other physicians and specialists from other medical fields
- Make sure you know what to do in case of emergencies!
  - Always ask for a ***contact phone number*** in case of any problems, new symptoms, or if you have any questions

"I couldn't diagnose this ailment on the internet so I was forced to come to you."

Artist: Ron Morgan

Summary/Conclusions

- MDS is a complex set of diseases that requires accurate diagnosis.
- Patient outcomes vary widely and treatment is tailored by risk scores.
- For patients with lower-risk disease, the goals of care are to improve number of times a patient needs a blood transfusion and improve quality of life/symptoms.
- The standard of care for higher-risk patients is azacitidine (Vidaza®) or decitabine (Dacogen®) with or without allogeneic stem cell transplantation.
- A variety of new agents are being evaluated in clinical trials for patients with MDS.

Thank You! Any Questions?

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