Myelodysplastic Syndromes

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Primary Objectives

- To review clinical presentation of MDS and differential diagnosis
- To review the epidemiology and diagnostic evaluation of patients with MDS
- To review insights into the pathogenesis of MDS
- To review treatment recommendations for patients with low and high risk MDS
- To discuss special cases: hypoplastic MDS, MDS with 5q deletion, MDS with Ringed Sideroblasts, ICUS/CHIP

Case

- 71 year old female with fatigue and neuropathy is referred to OSU for second opinion and concern for a marrow disorder.
- WBC 1.8 (10% segs), Hg 8.3g/dL, Plt 277
  - Bone marrow biopsy with dyserythropoiesis and dysmegakaryopoiesis, low blasts
  - Normal female karyotype

Case continued

- Exam findings:
  - Dentures in place
  - Severe sensory and motor neuropathy

Case continued

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  - Dentures in place
  - Severe sensory and motor neuropathy
- She mentioned that she had recently seen on ABC news a report of Zinc toxicity from Poligrip.
  - She stopped using the product about a month prior, but had used it for 4-5 years.

Case continued

- Her Zinc level was high at 2800ug/L in the urine with Zn/Cr ratio of 5456/ug/g creat (nl 100-900)
- Serum copper level is undetectable

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- Serum copper level is undetectable
- Copper replacement given, CBC normal within 3 weeks.

Differential Diagnosis: Non-Hematologic Causes of Cytopenia

- Reactive/Temporary Cause
  - Drug Effects
  - Infection (viral, bacterial, etc.)
- Nutritional Deficiencies
  - B12, folate, copper, iron
  - Alcoholism, liver dysfunction
- Autoimmune Disorders
  - Hypothyroidism
  - Rheumatologic Disorders

Case 2

- 63-year-old woman with no PMH presents to her internist for her first evaluation in 5 years to re-establish care.
  - She reported worsening fatigue worsening for about a year
  - Mild shortness of breath with activity
  - Occasional bruising but usually after an injury
- Exam: Notable for pallor, mild systolic murmur, and scattered small bruises

Laboratory Results:

Hgb	9.2g/dL
MCV	101
WBC	2.3
ANC	690/uL
Blasts	None
Platelet	64,000/uL

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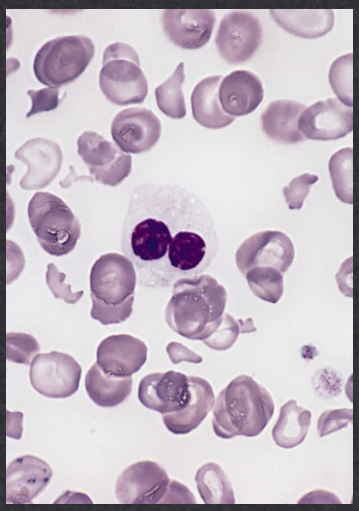
B12	810
Folate	20
Erythropoietin	254 (normal 2-20)

Diagnostic Work-Up

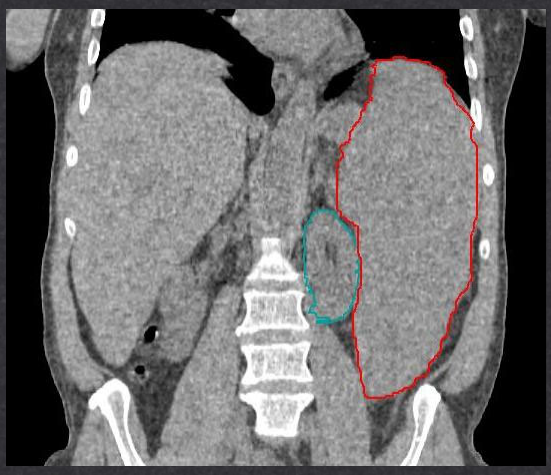
- Peripheral blood smear
- B12, folate, iron studies, copper level
- LDH, haptoglobin, DAT, retic count, epo level
- TSH
- HIV, Hepatitis B and C, and Parvovirus B19
- SPEP, PNH
- If symptomatic, possibly CT abdomen or ultrasound spleen
- Bone marrow biopsy including cytogenetics
- Hematologic neoplasm sequencing panel

Peripheral Smear



https://en.wikipedia.org/wiki/Myelodysplastic_syndrome#/media/File:Hypogranular_neutrophil_with_a_pseudo-Pelger-Huet_nucleus_in_MDS.jpg

Imaging



https://upload.wikimedia.org/wikipedia/commons/8/89/Tumor_Myelodysplastic_Spleen.JPG

Case continued

- Bone marrow biopsy returns consistent with MDS with 8% blasts.
- Cytogenetics show a complex karyotype with trisomy 8, deletion 7, and deletion of 20q
- Sequencing panel reveals mutations of ASXL1 and TET2

Epidemiology

- SEER officially began to track in 2001
  - 15,000 new diagnoses per year
  - Median age at presentation is 70
  - Incidence increases with age
    - < 40 years 0.14 per 100,000
    - ≥ 80 years 36 per 100,000
  - Male predominance

Epidemiology

- Risk factors
  - Age
  - Prior chemotherapy
    - Alkylating agent
      - 5-10 years – chromosome 5 and 7 abnormalities
    - Topoisomerase II inhibitors
      - 1-2 years – 11q23 abnormalities
    - XRT (5-10 years)
  - Benzene exposure (organic solvents)
  - Smokers exposed to environmental agents (OR: 1.45)

Prognostication

International Prognostic Scoring System (IPSS)

- Multivariate analysis of hematologic characteristics of 816 patients at diagnosis
  - Also included patients with 20-30% blasts
- Identified 3 variables
  - % of bone marrow blasts
    - <5%; 5-10%; 11-20%, 21-29%
  - Cytogenetic abnormalities
    - Good: Normal, -Y, del(5q), del(20q)
    - Poor: Complex (≥3 abnormalities); abnormal Chr 7
    - Intermediate: All others
  - Number of cytopenias
    - ANC < 1800; Hemoglobin < 10; Platelets <100,000

Greenberg P Blood 1997; 89: 29:2079

IPSS Scores and Associated Risk Groups

Risk Group	Score	Median Survival (years)	Median Time to AML evolution (years)
Low	0	5.7	9.4
Intermediate-1	0.5-1.0	3.5	3.3
Intermediate-2	1.5-2.0	1.2	1.1
High	≥2.5	0.4	0.2

Greenberg P Blood 1997; 89: 29:2079

Limitations of the IPSS

- Does not consider severity of cytopenias, just their presence
- Cytogenetic abnormalities were limited and not all patients are represented
- Not designed to use at later time points after diagnosis
- Excluded patients with secondary MDS, therapy-related MDS, and CMML
- Variability in outcomes of patients with lower risk disease

Revised International Prognostic Scoring System (IPSS-R)

- Cytogenetics (added 2 additional groups)
  - Very good: -Y or del(11q)
  - Good: CN, del(5q), del(12p), del(20q) or double abnormality including del(5q)
  - Intermediate: del(7q), +8,+19, i(17q) and any other single or double independent clones
  - Poor: -7, inv(3)/t(3q)/del(3q), double abnormalities including =7/del(7q) or 3 abnormalities
  - Very Poor: complex (≥3 abnormalities)
- Blast %
  - <2%, 2-5%, 5-10%, >10%
- Cytopenias
  - ANC, hemoglobin, and platelet count all now contribute to the score based on their severity

Greenberg PL Blood 2012; 120: 2454

Revised International Prognostic Scoring System (IPSS-R)

	Very Low	Low	Intermediate	High	Very high
Median Survival (years)	8.8	5.3	3.0	1.6	0.8
Median time to 25% AML transformation (years)	NR	10.8	3.2	1.4	0.73

Greenberg PL Blood 2012; 120: 2454

Case 2 continued

- IPSS score
  - Intermediate-2 risk group
  - Median survival of 1.2 years
- R-IPSS score
  - Very high risk group
  - Median survival of 0.8 years

Summary of Work-Up

- When to suspect?
  - Unexplained cytopenia
  - Symptoms may include fatigue, SOB, and bleeding or bruising depending on the cell lines involved
- Initial steps in diagnosis?
  - Comprehensive lab studies
  - Consider abdominal imaging if hepatosplenomegaly suspected
- When to refer to hematology?
  - New cytopenia and/or work-up has not shown source of cytopenia
  - If bone marrow biopsy felt to be indicated

Myelodysplastic Syndromes

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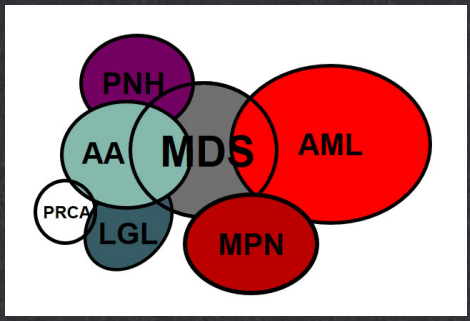
Pathogenesis and Treatment

MDS Overlaps with Other Entities



- MDS clinical and histopathological characteristics can overlap with many other hematological disorders
- An accurate diagnosis relies on expertise in interpreting diagnostic tests

Myelodysplastic Syndromes

- Heterogenous group of malignant hematopoietic stem cell disorders
- Characterized by clonal hematopoiesis
- Quantitatively and qualitatively abnormal myeloid differentiation
  - Chronic cytopenias
- Immune dysregulation
- Variable progression to AML

2016 WHO MDS Subtypes
MDS with single lineage dysplasia
MDS with multilineage dysplasia
MDS with Ringed Sideroblasts
MDS with RS with single lineage dysplasia
MDS-RS with multilineage dysplasia
MDS with isolated del(5q)
MDS with excess blasts
MDS-EB-1
MDS-EB-2
MDS, unclassifiable
With 1% blood blasts
With single lineage dysplasia and pancytopenia
Based on defining cytogenetic abnormality
Refractory cytopenias of childhood

Arber DA Blood 2016; 127:2391-2405

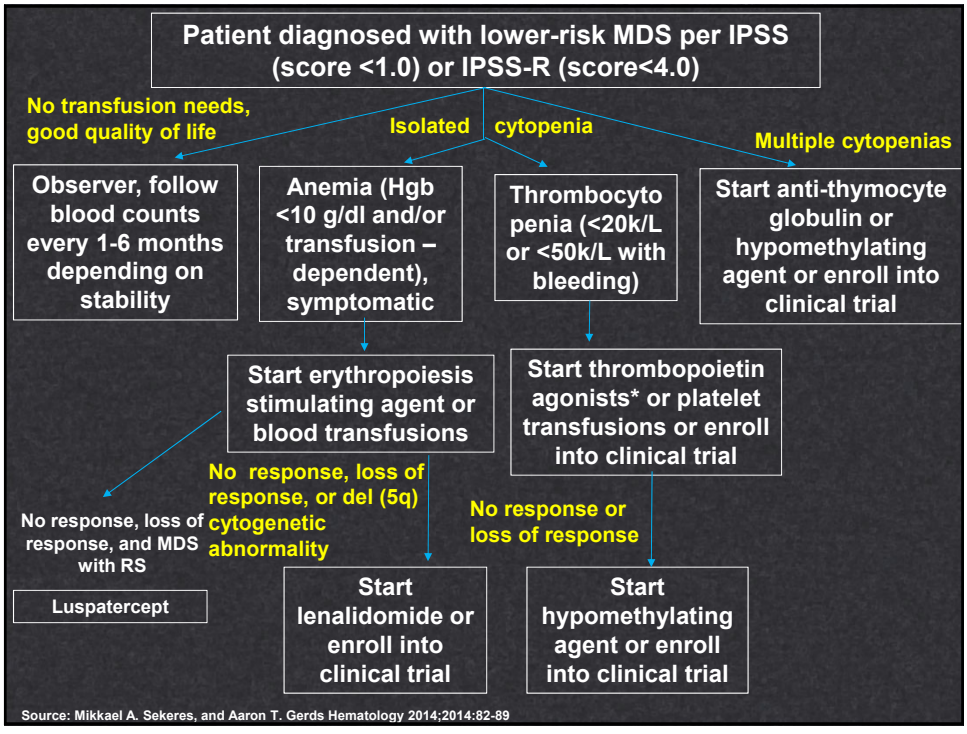
Chromosomal Abnormalities that diagnose MDS in Absence of definitive morphological criteria

Abnormality	Frequency, %
−5 or del(5q)	10-15
−7 or del(7q)	10
i(17q) or t(17p)	2-3
del(12p) or t(12p)	1-2
del(11q)	1-2
−13 or del(13q)	1-2
del(9q)	1
idic(X)(q13)	1
inv(3)(q21q26.2)	1
t(6;9)(p23;q34)	1
t(3;21)(q26.2;q22.1)	<1
t(1;3)(p36.3;q21.2)	<1
t(11;16)(q23;p13.3)	<1
t(2;11)(p21;q23)	<1

Pathogenesis

- Unclear (? becoming clearer)
  - Involves the stepwise acquisition of oncogenic driver mutations
    - Thought to derive from a single transformed hematopoietic progenitor cell
    - >90% cases are associated with ≥ 1 driver mutation
  - Immune dysregulation
  - Abnormal marrow microenvironment
  - Alterations in DNA methylation/histone function

Treatment


Patient diagnosed with lower-risk MDS per IPSS (score <1.0) or IPSS-R (score<4.0)
No transfusion needs, good quality of life
Isolated cytopenia
Multiple cytopenias
Observer, follow blood counts every 1-6 months depending on stability
Anemia (Hgb <10 g/dl and/or transfusion – dependent), symptomatic
Thrombocyto penia (<20k/L or <50k/L with bleeding)
Start anti-thymocyte globulin or hypomethylating agent or enroll into clinical trial
Start erythropoiesis stimulating agent or blood transfusions
Start thrombopoietin agonists* or platelet transfusions or enroll into clinical trial
No response, loss of response, and MDS with RS
No response, loss of response or del (5q) cytogenetic abnormality
No response or loss of response
Luspatercept
Start lenalidomide or enroll into clinical trial
Start hypomethylating agent or enroll into clinical trial
Source: Mikkael A. Sekeres, and Aaron T. Gerds Hematology 2014;2014:82-89

Anemia and Survival

- 1000 newly diagnosed patients with low and INT-1 risk MDS enrolled in European LeukemiaNet MDS registry (EUMDS)
  - 14 countries
  - Median age = 74 years
  - Most patients died without disease progression (higher risk/AML)
    - Infectious and cardiovascular
  - The mortality rate in transfusion dependent patients was 24% vs 5% in transfusion independent patients
    - Transfusion dependent patients with disease progression had a higher mortality rate than those who were not transfusion dependent at disease progression (66% vs 32%)
  - Transfusion dependent patients without disease progression and a serum ferritin $\geq$ 1000 µg/L had a higher mortality rate 56% vs 21% (HR 4.79, 95% CI 2.56-8.96) than transfusion independent patients
  - The degree of anemia appears to have an impact on OS and leukemia free survival

De Swart ASH Annual Meeting 2012; 120: 3830.

Erythropoietin Stimulating Agents

- Erythropoietin induces globin gene expression and promotes late erythroid differentiation
- Who responds?
  - Patients with lower risk MDS without ring sideroblasts had a higher probability of response
  - Higher response rates in patients without a prior transfusion need
  - Higher response in those with pre-treatment serum epo levels < 150-200

Serum Epo	Points	PRBCs/month	Points	Total Score	Likelihood of response
< 100	+2	< 2 Units	+2	> +1	74%
100-500	+1	> 2 Units	-2	-1 to +1	23%
> 500	-3			< -1	7%

Predictive model for response to erythropoietin and GCSF
Based on serum epo level and RBC transfusion requirement

Hellstrom-Lindberg E et al Br J Haem 2003; 120:1037-1046

Erythropoietin Stimulating Agents

- Response can take 8 weeks or more
- Duration of response and time to transfusion dependency is longer in patients treated within 6 months of diagnosis vs after 6 months
- Erythroid response to darbepoietin 56% at 24 weeks in lower risk MDS patients

Iron Overload

- Begins prior to patients becoming red cell transfusion dependent
  - Ineffective erythropoiesis suppresses hepcidin production in the liver → unrestrained intestinal iron uptake due to lack of inhibition of ferroportin (iron channel on basolateral surface of enterocytes)
- Iron toxicity may not only depend on the degree of iron accumulation but also on the extent of exposure to non-transferrin bound iron → increased oxidative stress

Malcovati L et al Haematologica 2006; 91: 1588-90

Iron Chelation

- Above a serum ferritin of 1000 ng/mL there is a dose dependent impact on OS 30% greater risk of death for every 500ng/mL increase in ferritin above 1000 ng/mL
- Recommendations for chelation are mostly based on expert opinion
  - Patients with a transfusion history of at least 20 or 25 units of PRBCs and serum ferritin > 1000
  - Focus on patients with lower-risk MDS who may have a longer life expectancy and will therefore receive long-term transfusion therapy
  - MRI is able to diagnose iron overload

Higher Risk Patients

- Early initiation of hypomethylating agent
  - Azacitidine or decitabine
  - CR rate of approximately 20%
  - 21 months versus 13 months of AML transformation when compared to Best Supportive Care
- Screen for HLA matched donor at diagnosis
  - Nonmyeloablative conditioning given age
  - Eligibility depends on preserved organ function, performance status, etc

Role of Allogeneic transplantation

- 3rd most common indication for allogeneic stem cell/bone marrow transplantation
- Cutler et al. developed decision model to understand how treatment decisions affect overall outcome in patients with newly diagnosed MDS
  - Low/Int-1 IPSS patients – delay until progression
  - Int-2/High risk IPSS patients – early transplantation

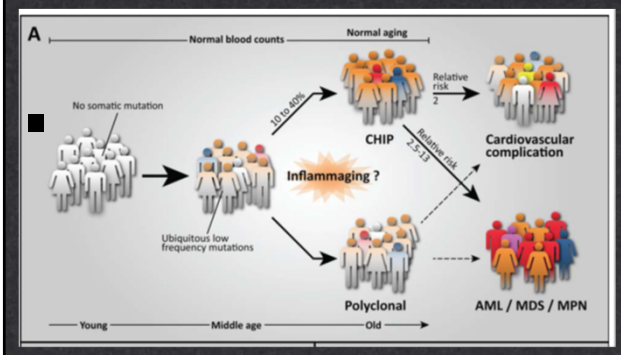
Cutler et al. Blood. 2004 104: 579-585

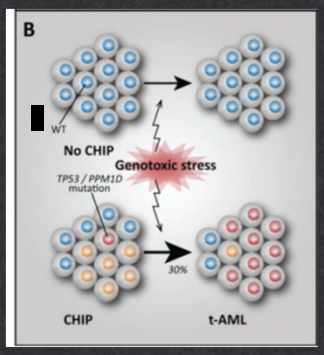
Special Case

- A 52 year old female was found to have a new diagnosis of Stage III breast cancer and due to history of high risk family cancer, she sought genetic counseling.
- She underwent testing which included next generation sequencing of the blood.
- Results showed a *DNMT3A* mutation and her peripheral blood counts were normal at time of testing
- This result was consistent with Clonal Hematopoiesis of Indeterminate Potential (CHIP)

HP2

Clonal Hematopoeisis of Indeterminate Potential





Condition characterized by the presence of a somatic mutation associated with a hematologic malignancy in the absence of definitive diagnostic criteria for neoplasm

Busque, L., Buscarlet, M., Mollica, L. and Levine, R.L. (2018), Concise Review: Age-Related Clonal Hematopoiesis: Stem Cells Tempting the Devil. Stem Cells, 36: 1287-1294. doi:10.1002/stem.2845

Idiopathic cytopenias of undetermined significance (ICUS)

- Describes patients in whom MDS is possible but not proven
- Must have relevant cytopenia in one or more lineage *hemoglobin <11 g/dL, neutrophil count <1500, platelet count <100,000 that persists for 6 months, cannot be explained by other disease and does not meet diagnostic criteria of MDS
- Patients should be carefully monitored

Slide 43

HP2 Janis - CHIP is more of a condition than a test, so I think this belongs in On Target (do we need to label all slides?)
Harty, Patrick, 5/21/2020

Special case continued

- She underwent treatment for her breast cancer with systemic chemotherapy and surgery.
- Approximately 5 years later, she began developing pancytopenia with WBC of 1.5, Hgb 10.0, and platelet count of 89,000. Her MCV was 105.
- She underwent a bone marrow biopsy for work-up and was consistent with MDS-EB-1 with 9% blasts.
- Cytogenetics were complex with NGS showing a new *TP53* mutation along with her known *DNMT3A* mutation.
- Diagnosis was consistent with therapy-related MDS and patient was initiated on azacitidine

Special case continued

- The patient underwent bone marrow re-assessment after 2 cycles of therapy and was found to have progression to AML with 24% blasts.
- Bone marrow biopsy showed no change in cytogenetics or NGS results from prior testing.
- She is now undergoing treatment with liposomal daunorubicin and cytarabine for AML with MDS-related changes.

Conclusions

- MDS is a heterogeneous disease
  - Mutational analysis will likely improve our ability to risk stratify patients better and potentially give more targeted therapeutics
- Consideration of ESA therapy in patients with low risk disease with anemia only is reasonable
- Consider lenalidomide in patients with 5q abnormalities
- Consider luspatercept in MDS with Ringed Sideroblasts who are transfusion-dependent and not/lost response to ESA therapy
- 5-azacytidine is the only available hypomethylating agent with a proven survival advantage
- Consider BMT referral in patients with higher risk disease