An Overview of Myelodysplastic Syndromes (MDS)

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OBJECTIVES

› Discuss Incidence & Risk Factors for MDS
› Describe the pathogenesis & clinical presentation
› Describe the diagnosis & prognosis of MDS
› Discuss the treatment options & supportive care for MDS

Multi-Discipline Approach

› MDs/PA/NS & Consulting Services
› RNs/CNAs/HUCs
› Pharmacy
› Social Services
› Chaplaincy
› PT/OT/SLP
› Nutritional Services & Wound Care
› Palliative Care/Hospice/Volunteers
The myelodysplastic syndromes (MDS) comprise a heterogeneous group of malignant hematopoietic stem cell disorders characterized by dysplastic and ineffective blood cell production (cytopenias).

MDS has a variable risk of transforming to acute leukemia.

Patient’s can have varying degrees of reduction in RBCs, platelets and mature WBCs (qualitative and quantitative).

These abnormalities often result in symptomatic anemia, bleeding, and increased risk of infection.

The number of people diagnosed with myelodysplastic syndromes (MDS) in the United States each year:

- Some estimates ~ 10,000/year
- Other estimates have been much higher
- The number of new cases diagnosed each year is likely increasing as the average age of the US population increases.
Risk Factors
- Older age → MDS is uncommon in people younger than 50, and most cases are found in people in their 70s or 80s
- Males > Females
- Prior chemotherapy (+ radiation) → “Secondary” MDS
- Stem cell transplants
- Familial MDS (due to gene mutation)
- Genetic syndromes
- Smoking
- Environmental exposure
  - High dose radiation (nuclear reactor, atomic bomb blast)
  - Benzenes & certain chemicals in petroleum/rubber industries

Pathogenesis of MDS
- Incompletely understood ??
- Like other cancers, it involves the stepwise acquisition of oncogenic mutations that may arise:
  1. De novo
  2. Secondary to risk factors (previous slide)
- MDS that develops after treatment with chemotherapy may also develop from the selection of pre-existent chemotherapy-resistant clones (e.g., those with mutations of TP53)

Clinical Presentation
- Non-specific: asymptomatic or symptomatic
- Anemia: most common symptomatic presentation
- Thrombocytopenia: bleeding/bruising
- Infection: neutropenia and/or impaired granulocyte function
  - Predominantly bacterial, skin is most common site
  - Although fungal, viral, and mycobacterial infections can occur, they are rare in the absence of concurrent administration of immunosuppressive agents.
- Autoimmune disorders (25%) → RA, RHS, PMR
- Acquired Hgb H disease
- Skin manifestations: Sweet Syndrome → acute febrile neutrophilic dermatosis
**Work-Up & Diagnosis of MDS**

- **History and Physical**
- **CBC with differential, Peripheral Smear**
- Rule out other causes of anemia (TSH, LDH, B12/Folate, Fe, Cu)
- **Bone marrow aspirate & biopsy**
  - Iron stain/ringed sideroblasts
  - Conventional chromosomes (FISH if < 20 optional metaphases)
  - Flow Cytometry to evaluate for large granular lymphocyte (LGL) or paroxysmal nocturnal hemoglobinuria (PNH)
  - Consider genetic/molecular testing
- **Serum erythropoietin (prior to RBC transfusion)**

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**Diagnostic Criteria (1 of 2)**

- Otherwise unexplained quantitative changes in one or more of the blood and bone marrow elements. The values used to define cytopenia are:
  - Hemoglobin <10 g/dL (100 g/L);
  - Absolute neutrophil count <1.8 x 10^9/L (<1800/microL);
  - Platelets <100 x 10^9/L (<100,000/microL).

- However, failure to meet the threshold for cytopenia does not exclude the diagnosis of MDS if there is definite morphologic evidence of dysplasia.

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**Diagnostic Criteria (2 of 2)**

A. **Significant dysplasia** (≥10 percent of erythroid precursors, granulocytes, or megakaryocytes) upon visual inspection of the peripheral blood smear, bone marrow aspirate, and bone marrow biopsy in the absence of other causes of dysplasia, **OR**

B. **Increased blasts** (5-19%), **OR**

C. Evidence of chromosome clonality (not AML)

- Without any of the above = Idiopathic Cytopenias of Undetermined Significance (**ICUS**)
Differential Diagnoses

- MDS characterized by dysplasia and cytopenias
- ICUS idiopathic cytopenias of undetermined significance
- AML MDS as above, but > 20% blasts (WHO), or specific cytogenetic abnormalities diagnostic of AML
- Myelodysplastic/Myeloproliferative (MDS/MPN) In contrast, the (MDS/MPN) neoplasms include disorders where both dysplastic and proliferative features coexist
  1. Chronic myelomonocytic leukemia (CMML)
  2. MDS/MPD with ringed sideroblasts and thrombocytosis
- Myelofibrosis
- Aplastic Anemia
- HIV infection, poor nutritional status, medications

WHO (2017) → MDS Subtypes

Dependent upon multiple factors:
  - # of dysplastic lineages, cytopenias, % ringed sideroblasts, BM and PB blasts, conventional cytogenetics
  1. MDS with single lineage dysplasia
  2. MDS with ringed sideroblasts
  3. MDS with multilineage dysplasia (< 5% BM blasts)
  4. MDS with isolated del (5q)
  5. MDS with excess blasts (5-19% BM blasts)
  6. MDS Unclassifiable

MDS Bone Marrow Cytogenetics

- 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.
Somatic mutations are common in MDS

IPSS-R does not take into account somatic mutations

Several mutated genes have prognostic significance, independent of IPSS-R

There is no agreed-upon standard treatment approach for patients with symptomatic MDS, with the probable exception of lenalidomide

1. in RBC transfusion-dependent patients
2. with deletion 5q
3. Low or Intermediate-1 MDS
Treatment Overview

- **Encourage Clinical Trials**
- **Main goals of treatment:**
  1. control symptoms due to cytopenias
  2. improve quality of life
  3. minimize the toxicity of therapy
- **Consider performance status and patient values**
- **Take into account MDS Risk → IPSS-R**
- **Consider immediate treatment for symptomatic cytopenias** (anemia, thrombocytopenia, neutropenia with recurrent infections)

Treatment Options (Higher Risk)

- **Allogeneic Transplant Candidate?**
  - **Yes → ASAP** (bridge with hypomethylating agent or even AML induction)
  - **No → hypomethylating agent**
  - The only cure, but high risk vs high reward
  - Transplant Center — away from home extended period
  - Risk for GVHD, “trading in 1 disease for another”
  - Prolonged immunosuppressive therapy (IST)
  - Increased infectious risk

Hypomethylating Agents - HMA

- **General**
  - Time to response 3-4 months/cycles
  - Overall response rates = 45-50%; CR=7-17%
  - Median duration of response = 12-18 months
- **Azacitadine**
  - Favorable factors = female, Age<60, better risk chromosomes, < 10% blasts, some response to treatment
  - 2 year overall survival = 15%
  - Median OS after fails therapy = 5.6 months
- **Decitabine**
  - Median OS after fails therapy = 4.3 months
- **Guadecitabine**
The optimal approach for reducing red blood cell (RBC) transfusion needs in patients with lower-risk myelodysplastic syndromes (MDS) is unknown.

- **Luspatercept** is an erythroid maturation agent that can improve anemia in MDS with ring sideroblasts (MDS-RS) by enhancing late-stage erythropoiesis.
- In preliminary results from a phase III study of over 200 patients with lower-risk MDS-RS, luspatercept reduced RBC transfusion-dependence compared with placebo after eight weeks (38 versus 13 percent, respectively) and 12 weeks (28 versus 8 percent).
- Luspatercept was well tolerated, with low rates of myalgia, increased blast count, and general physical decline.
- Under review by the US FDA for lower-risk MDS.

Future targeted therapies → “mutations”

- **Immunotherapy** – “Checkpoint Inhibitors”
  - Not monotherapy
  - In combination with HMAs → Phase II trial

Clinical Trials

Supportive Therapy

- **Anemia (symptomatic)**
  - Erythropoietin Stimulating Agents (ESA) → Epoetin alfa and Epoetin alfa-epbx (Darbepoetin alfa)
  - Indicated for Hgb<10, EPO <500, Not 5q-

- **Neutropenia**
  - Filgrastim, filgrastim-sndz, tbo-filgrastim
  - Not recommended for routine prophylaxis
  - Consider in neutropenic patients with recurrent infections

- **Thrombopoietin-receptor agonist**
  - Consider in lower-risk MDS or with severe life threatening thrombocytopenia
  - Trials of thrombopoietin mimetics are ongoing
Supportive Therapy

- **Antibiotics**
  - Routine prophylaxis is **not** recommended unless patient has a bacterial infection or is having recurrent infections

- **Iron chelation**
  - If > 20-30 RBC transfusions, consider daily deferoxamine, particularly in low-risk patients or if candidate for transplant
  - Tx if ferritin > 2500, goal to get below 1000
  - Do not treat with deferoxamine if CrCl < 40 mL/min

- **Transfusions…**

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**EH RBC Transfusion Guidelines**

1. Hgb 7.0 gm or less
2. Acute blood loss not responding to volume resuscitation
3. Hgb 7.0 gm or less for stable hospitalized patients
4. Hgb 8.0 gm or less for patients with preexisting cardiovascular disease; oncology patients actively under treatment; or higher Hgb. levels if symptoms are present
5. Hgb 8.0 gm or less for perioperative surgical patients; higher Hgb levels if symptoms are present
6. For non-bleeding patients, RBC transfusions should be ordered one at a time with reassessment of Hgb and clinical status prior to ordering additional units (exception for oncology outpatient transfusions)

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**EH Platelet transfusion Guidelines**

1. Platelet count <10,000 in stable, nonbleeding patients
2. Platelet count <50,000 with bleeding or pre-procedure, or for neonates
3. Platelet count <100,000 with bleeding requiring RBC transfusion, or neuraxis procedures or ocular procedures
4. Bleeding and platelet dysfunction or documented prolonged platelet function assay
5. Platelet replacement in Massive Transfusion
6. Platelets are not recommended for: TTP, Post Transfusion Purpura, Hemolytic Uremic, Syndrome, HELLP Syndrome
Known Transfusion Risks

- **INFECTION DISEASE RISK PER UNIT**
  - Hepatitis C 1 in 1.1 million
  - Hepatitis B 1 in 800,000 to 1.2 million
  - HIV 1 in 1.5 million
  - Bacterial Contamination
    - 1 in 100,000 platelets
    - 1 in 5 million red cells
  - *Other infectious diseases (i.e. HTLV, West Nile Virus)* have been reported at extremely low frequencies.

- **NON-INFECTIOUS COMPLICATION RISK PER UNIT**
  - ABO Incompatible Transfusion 1 in 40,000
  - Acute Hemolysis 1 in 76,000
  - Fatal Acute Hemolysis 1 in 1.8 million
  - Delayed Hemolysis 1:2,500-1:11,000
  - Febrile Non-Hemolytic Reaction 1:100 to 1:1,000
    - with universal leukoreduction
  - Hives 1:33-1:100
  - Acute Lung Injury (TRALI) 1:1,200-1:190,000
  - Anaphylaxis 1:20,000-1:50,000
  - Circulatory Overload <1%
  - Graft-vs-Host Disease (Rare)

End of Life

- **Transition**
  - Transformation to AML
  - Increased transfusion requirements
  - Ethical dilemma? ~ $800 per unit

- **Hospice**
  - Transfuse on an as needed basis → this is a major change of care plan for patient
  - Hospice gets about $4500 per month/patient
  - Quality of life ~ live longer
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