What are my Options with High Risk MDS/AML?

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Our Mission

The Aplastic Anemia & MDS International Foundation is the world's leading nonprofit health organization dedicated to supporting patients and families living with aplastic anemia, myelodysplastic syndrome (MDS), paroxysmal nocturnal hemoglobinuria (PNH), and related bone marrow failure diseases. The Foundation provides answers, support, and hope to thousands of patients and their families around the world.

We are a patient-focused, patient-centered organization, serving patients and families throughout the three phases of bone marrow failure diseases:

- the life changing phase of diagnosis
- the life threatening phase of treatment
- the life long phase of living with a chronic disease
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1. Use the Q & A box on the bottom of your screen. Type your question into the box and press **ENTER**.
2. Please do not include private health information about the patient in your question. Our presenters cannot answer specific questions related to your diagnosis or treatment.
3. We will try to answer all questions during the webinar but may not be able to get to everyone.
4. If we do not get to your question, please send it to us via email at help@aamds.org, by calling the office at (800) 747-2820 x2 or by sending us a message on social media.
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• For up-to-date guidance, webinar links, resources and Frequently Asked Questions on COVID-19, visit www.aamds.org/education/covid-19

• Contact AAMDSIF via e-mail to help@aamds.org

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The AAMDSIF Medical Advisory Board and Staff are here to help you and your family, as we have for the past 36 years.
HIGH RISK MDS TO AML

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APRIL 10, 2021
WHAT IS IN BLOOD AND WHERE DOES IT COME FROM

Red blood cells carry oxygen throughout the body.

White blood cells help fight infections.

Platelets help control bleeding.

Spongy bone (contains red marrow)

Yellow marrow

Compact bone

Bone Anatomy

Blood vessels in bone marrow

Blood stem cell

Red blood cells

White blood cells

Platelets

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Courtesy of CureSearch and NCI
BONE MARROW STEM CELL HIERARCHY

ANYTHING CAN GO WRONG WITH THE BONE MARROW STEM CELL “FAMILY TREE”
GENETICS OF MDS

MDS mutation landscape

- **Proliferation**
  - JAK2 3%
  - BRAF <1%
  - GNAS <1%
  - KRAS 1%
  - NRAS 4%
  - CDKN2A <1%
  - CBL 2%
  - PTPN11 <1%

- **Impaired differentiation**
  - RUNX1 5%
  - ETV4 3%
  - SETBP1 7%

- **Epigenetic regulation**
  - ASK1 14%
  - DNAH3A 8%
  - EZH2 6%
  - IDH1/2 2%
  - TET2 21%
  - UTX 1%
  - ATRX <1%

- **Pre-mRNA splicing**
  - SF3B1 22%
  - SF3A1 <1%
  - PRPF40B 1%
  - U2AF1 8%
  - ZRSR2 5%
  - SRSF2 11%
  - U2AF65 <1%

- **Other**
  - NPM1 2%

- **IPSS independent good prognosis**

- **IPSS independent poor prognosis**

WHY MDS HAPPENS:

IT’S NOT ALL GENETICS

MANY FACTORS ARE CULPABLE FOR MDS
IMMUNE DYSREGULATION IN MDS

Low-risk disease: \( \uparrow \) immune activation
- Less regulatory immune cells
- Immune cells are more aggressive and attack the corrupted bone marrow stem and progenitor cells
- More inflammation and increased bone marrow cell death

Late-stage, high-grade disease: \( \downarrow \) immune activation
- More regulatory immune cells that “turn off” the immune system
- Dysfunctional immune cells
- Less inflammation and reduced bone marrow cell death

\( \uparrow \) immune activation \( \rightarrow \) \( \uparrow \) MDS progression and leukemia proliferation
TREATMENTS VARY BASED ON HOW AGGRESSIVE THE MDS IS

For low grade disease:
- Observation
- Transfusions
- Growth factors to boost blood cell counts
- Lenalidomide
- Immune suppression

For high grade disease:
- Only curative option is bone marrow stem cell transplant
- Hypomethylating agents (HMAs): decitabine, azacitidine
TRANSFUSIONS AND IRON CHELATORS

- 40% in lower-risk patients and 60% to 80% in higher-risk patients need transfusions
- Patients receiving regular transfusions have inferior survival compared with those who do not require transfusions
- RBC transfusions should be minimized and utilized only as necessary for symptomatic anemia or to maintain a safe hemoglobin of 7 to 8 g/dL
- Iron chelation therapy with oral deferasirox or parenteral deferoxamine can be considered in patients with a relatively good MDS prognosis who have evidence of tissue iron overload or elevated blood iron levels

Courtesy of New Atlas
GROWTH FACTORS

- Studies with recombinant ESAs (epoetin and darbepoetin) increase RBC production in 20-40% of patients.
- An 8- to 12-week trial of an ESA at standard dosing schedules is appropriate for anemic patients.
- G-CSF (filgrastim, tbo-filgrastim) have been evaluated in patients with MDS and increase the neutrophil/white blood cell counts in up to 60% to 90% of patients, which may help some patients who have recurrent infections.
  - This practice is discouraged overall as survival was shorter in patients with “higher levels of pre-leukemia.”
- TPO receptor agonists (thrombopoiesis-stimulating agents) can raise the platelet count in some patients with MDS and decrease platelet transfusions and bleeding events.
  - Not FDA approved for MDS.
  - Increases pre-leukemic cells, accelerates progression into full blown leukemia by 3-fold, esp in patients with higher risk disease!
LENALIDOMIDE & IMMUNE MODULATORS

- Lenalidomide is an immune modulator
- In certain types of MDS, 67% of patients on lenalidomide achieved transfusion independence
- Responses typically occur after 4 weeks with responses lasting more than 2 years
- Hemoglobin on average rise by over 5 g/dL
- If lenalidomide is given to all MDS patients then response rates fall
  - Only 26% of patients became red blood cell transfusion independent with a duration of response of no more than 10 months
HYPOMETHYLATING AGENTS (AZACYTIDINE, DECITABINE)

- **Classical mechanism of action:** activation of cancer-fighting, tumor suppressor genes

- **Alternative mechanisms:**
  - Induces a more effective inflammatory response by the immune system
  - Encourages the most healthy stem cells to divide and differentiate into mature, functional blood and immune cells

- 17% of patients achieved a complete response
- 15% achieved a significant reduction in leukemia cells
- 18% experienced improvement in blood cells counts
- Clinical response requires at least 4-6 months of treatment
<10% of patients with MDS currently undergo transplant due to older age, comorbid conditions

- Relapse rates are up to 50% even with transplant
- Reduced-intensity conditioning regimens (less chemo and radiation) is allowing for older, sicker patients to get transplants
  - Lower transplant-related mortality but higher relapse rate
  - Overall survival to more aggressive chemo, radiation conditioning
IF MDS → AML: CHEMOTHERAPY

- Induction therapy (inducing a complete remission [CR])
  - 7 days of infusional cytarabine and 3 days of an anthracycline chemotherapy ("7+3")
  - CR in 60 to 85% of adults who are 60 years or younger
  - Patients older than 60 years have worse outcomes

- Consolidation therapy (preventing relapse)
  - Cytarabine chemo for 2-4 months
  - Bone marrow stem cell transplant
VYXEOS FOR THE FIT ELDERLY (S/T AML)

- VYXEOS is 7+3 encapsulated in “fat molecules”

- Vyxeos significantly improved median overall survival versus 7+3 (9.56 v 5.95 months)

- CR rates: 47.7% v 33.3%, favoring Vyxeos

- Early mortality rates with Vyxeos only 6%
AML IN THE GERIATRIC POPULATION

- Median survival 8-12 months in the best circumstances
- High frequency of genetic and chromosomal abnormalities
- No standard of care
- Hypomethylating agents can be considered
  - Can achieve CR in 10%-20% of patients
- Consider clinical trial for elderly with poor performance status or extensive co-morbidities
CR of 73% when combined with hypo-methylating agents

The median duration of CR is 11 months

Average survival almost 15 months

The most frequent side effects were low white blood cell counts, infections, diarrhea, fatigue
CONCLUDING REMARKS

- It’s not all genetics
- MDS stems from “inflamm-aging”
- MDS can be classified into low-grade vs aggressive/high-grade forms
- Aggressivity of MDS is associated immune “down-regulation” → less immune surveillance allows leukemia to proliferate
- Treatments for MDS include transfusions, growth factor support, immune modulation, HMA
- **Only curative option for MDS is bone marrow transplant**
- If MDS evolves into AML, treatment options include chemotherapy for fit patients or targeted agents with HMA for less fit patients
REFERENCES

THANK YOU! QUESTIONS?
TODAY: After the Conference! Virtual Support Groups!
4:00pm Eastern / 1:00pm Pacific
Aplastic Anemia - MDS – PNH – Caregivers
https://us02web.zoom.us/j/87341004741
Passcode: 2021

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