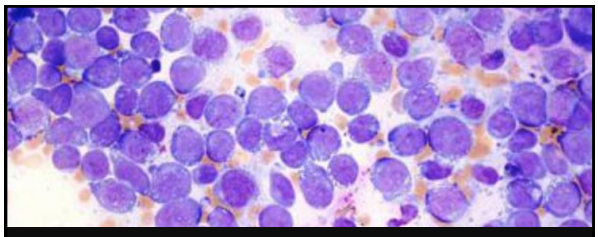

# MDS: Understanding Your Diagnosis and Treatment Options

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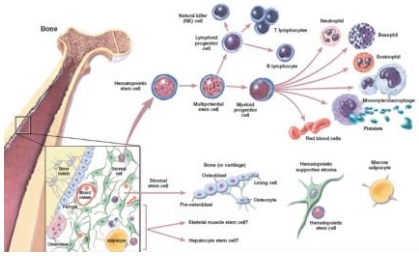
AA-MDS

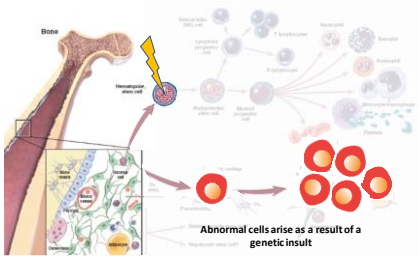
## Objectives

- Discuss the disease biology of
  - Myelodysplastic syndrome (MDS)
  - Acute myeloid leukemia (AML)
  - Chronic myelomonocytic leukemia (CMML)
  - Myeloproliferative Neoplasms (MPNs)
- Explore general treatment recommendations for each
- Understand when to consider stem cell transplantation (bone marrow transplant)

## Normally….




## Genetic mutations alter hematopoiesis




## Cancerous cells out-compete normal cells

## Clinical Findings

- There is limited space in the bone marrow.
- Cancerous cells suppress normal, healthy cells that make white blood cells, red blood cells, and platelets.
- As a result, people with these diseases may have low blood counts, and even need transfusions, in spite of having many cells in their bone marrows.

## Clinical Findings (cont)

**Signs and symptoms are driven by the low blood counts**

- Low red blood cells (anemia)
  - Feel tired, appear pale
  - Reduced exercise tolerance
- Low white blood cell count (leukopenia/neutropenia)
  - Susceptible to infections
- Low platelets (thrombocytopenia)
  - Easy bruising, bleeding from nose, gums, etc.

## Who is affected

- Men and women
- Older people more often than younger people
- May be primary/*de novo* versus secondary to a prior genomic insult (chemotherapy, radiation therapy)
- Some are low-grade and require only observation while others necessitate aggressive treatment

## Treatment depends on

- Patient
  - Age
  - Motivation
  - Preference/treatment goals
  - Physical fitness (performance status)
  - Other medical conditions (co-morbities)
- Disease
  - Low- vs. high-risk disease
  - Tempo of the disease
  - Targetable mutations (if any)
  - Availability of research studies

## Treatment options by disease

- Myelodysplastic Syndrome (MDS) & Acute myeloid leukemia (AML)
- Chronic myelomonocytic leukemia (CMML)
- Myeloproliferative neoplasms (MPNs)

## Treatment options by disease

- **Myelodysplastic Syndrome (MDS) & Acute myeloid leukemia (AML)**
- Chronic myelomonocytic leukemia (CMML)
- Myeloproliferative neoplasms (MPNs)

## Identifying the "risk" of disease

- MDS and AML are heterogeneous diseases and tailored therapy is important.
- Use the International Prognostic Scoring System (IPSS) and Revised International Prognostic Scoring System (IPSS-R) to assess risk in MDS.
- In AML, use cytogenetics, molecular testing, primary vs. secondary, WBC at diagnosis, remission status, age, and other factors.

## Identifying the "risk" of disease (MDS)

IPSS-R Prognostic Risk Categories/Scores*

| RISK CATEGORY | RISK SCORE |
|---|---|
| Very Low | <=1.5 |
| Low | >1.5 - 3 |
| Intermediate | >3 - 4.5 |
| High | >4.5 - 6 |
| Very High | >6 |

IPSS-R: Prognostic Risk Category Clinical Outcomes*

| | No. pts | Very Low | Low | Intermediate | High | Very High |
|---|---|---|---|---|---|---|
| Patients (%) | 7012 | 19% | 38% | 20% | 13% | 10% |
| Survival*** | | 8.8 | 5.3 | 3.0 | 1.6 | 0.8 |
| AML(25%)***,† | | NR | 10.8 | 5.2 | 1.4 | 0.7 |

## Management of MDS

- Goals of treatment:
  1. Do no harm.
  2. Prevent transformation to AML, reduce transfusion dependence, and improve quality of life.
- Low-risk disease
  - May not need to do much.
- High-risk disease
  - May need aggressive therapy including stem cell transplantation/bone marrow transplantation

## Management of MDS

- Low-risk disease (fit/unfit patient, +/- comorbid conditions)
  - May not need to do much.
  - Best supportive care (observation, growth factors, etc)
- High-risk disease (unfit patient, many comorbid conditions)
  - Hypomethylating agents (azacitidine/decitabine)
  - Clinical trails
  - Best supportive care (transfusions)
- High-risk disease (fit patient, otherwise healthy)
  - May benefit from aggressive therapy, stem cell transplantation

## Management of MDS

- Azacitidine/decitabine are good drugs
  - In studies of high-risk MDS patients, azacitidine was better than current standard of care.
  - In compassionate use program 17% of patients had a complete remission or partial remission and 21% had hematologic improvement (almost 40% responded)
- Not great long-term solutions.
  - Responses tend not to be durable and we do not expect patients to be cured with this approach.

## Initial management of AML

Risk of Treatment

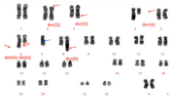
- Young/fit people:
  - Goal is to eliminate leukemia and get person into remission (CR)
  - "Induction therapy" with 7+3, clinical trial
- Older/fit people, otherwise healthy
  - Same goal
  - Induction therapy. Clinical trial may be preferred
- Older, unfit people with comorbid conditions
  - Less intensive therapy/best supportive care may be more appro
  - Consider palliative care

## Subsequent management of AML

- Pretty good at getting people into remission.
- Without additional treatment, virtually everyone will have their disease return.
- The type of treatment (consolidation) depends on the "risk" of the disease.

## Identifying the "risk" of disease (AML)

Cytogenetics:

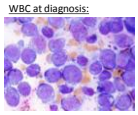


45,XX,t(2;3),t(4;8),del(6q),der(6q),-7

Molecular testing:
NPM1, CEBPA
FLT3-ITD

Chemo-refractory disease:
# of lines of chemotherapy needed to get into remission

WBC at diagnosis:



History of preceding MDS

Age:

Prior chemo/radiation therapy:

## Method of consolidation depends on risk

| Risk Status | Cytogenetics | Molecular Abnormalities |
|---|---|---|
| Better | inv(16)[a] or t(16;16)[a]<br>t(8;21)[a]<br>t(15;17) | Normal cytogenetics, with *NPM1* mutation or isolated *CEBPA* mutation in the absence of *FLT3* |
| Intermediate | Normal<br>+8<br>t(9;11)<br>Other non-defined | t(8;21), inv(16), t(16;16): with c-KIT[b] mutation |
| Poor | Complex (three or more abnormal clones)<br>−5, 5q−, −7, 7q−<br>11q23–non t(9;11)<br>inv(3), t(3;3)<br>t(6;9)<br>t(9;22)[a] | Normal cytogenetics: with *FLT3*-ITD mutation[c] in the absence of *NPM1* mutation |

High WBC at diagnosis
Prior MDS or chemo/radiotherapy
Chemo-refractory disease
Older patients (controversial)
Second remission

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Consolidation with chemotherapy:
- Usually high- or intermediate-doses of cytarabine
- Given in monthly cycles for up to four months

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Stem cell transplantation (preferred):
- If healthy, physically fit, and donor available

If not a transplant candidate/no donor:
- May consider consolidation, maintenance therapy with chemotherapy
- Observation

## Method of consolidation depends on risk

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High WBC at diagnosis
Prior MDS or chemo/radiotherapy
Chemo-refractory disease
Older patients (controversial)
Second remission

Consolidation with chemotherapy:
- Usually high- or intermediate-doses of cytarabine
- Given in monthly cycles for up to four months

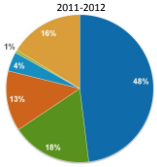
Controversial
- Guided by patient/provider discussions
- Chemotherapy vs. transplantation

Stem cell transplantation (preferred):
- If healthy, physically fit, and donor available

If not a transplant candidate/no donor:
- May consider consolidation, maintenance therapy with chemotherapy
- Observation

## SCT outcomes are not as great as we'd like

Post-Transplant causes of death
Matched related donor
2011-2012

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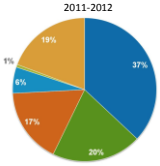


CIBMTR

## SCT outcomes are not as great as we'd like

- Newer targeted therapies allowing deeper pre-SCT remissions
- Maintenance therapy after transplant
- Transplant itself is safer than ever before

## Treatment options by disease

- Myelodysplastic Syndrome (MDS) & Acute myeloid leukemia (AML)
- **Chronic myelomonocytic leukemia (CMML)**
- Myeloproliferative neoplasms (MPNs)

## CMML

- CMML can be thought of as a combination of MDS and MPN
  - Monocytes in the blood
  - Dysplasia in the bone marrow
  - Low blood counts (cytopenias)
  - Big liver/spleen (hepatosplenomegaly)
- May progress to AML

## CMML

- Tends to be a disease of older people (median age 65 to 75 years)
- Male predominance
- 3 out of 1,000,000 people will be diagnosed with CMML every year

## CMML

- CMML-0
  - < 2% blasts in the blood and <5% blasts in the bone marrow
- CMML-1
  - 2-4% blasts in the blood and 5-9% blasts in the bone marrow
- CMML-2
  - 5-19% blasts in the blood and 10-19% blasts in the bone marrow
  - Presence of one or more Auer rods

## Treatment (CMML)

- Standard of care medications/chemotherapy do not reliably (durably) help and data to guide practice is limited due to rarity of disease.
  - **Azacitidine/decitabine**: Response rates of 67% (CR: 50%) but patients invariably lose response.
  - **Hydroxyurea**: Works by suppressing the bone marrow (good & bad)
- Clinical trials should be considered (if available).

## Treatment (CMML)

- Stem cell transplantation is the only curative option to date.
- Not a lot of data to guide decision-making and current studies are limited to highly selected, young/fit patients
- Survival at 3-5 years is 18-40%

## Treatment options by disease

- Myelodysplastic Syndrome (MDS) & Acute myeloid leukemia (AML)
- Chronic myelomonocytic leukemia (CMML)
- **Myeloproliferative neoplasms (MPNs)**

## Myeloproliferative Neoplasms

- Chronic myeloid leukemia (CML)
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
  - PMF, prefibrotic/early stage
  - PMF, overtly fibrotic phase
- Essential thrombocythemia (ET)
- Chronic eosinophilic leukemia, not otherwise specified (NOS)
- MPN, unclassifiable

## Myeloproliferative Neoplasms

- **Chronic myeloid leukemia (CML)**
- Chronic neutrophilic leukemia (CNL)
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  - PMF, prefibrotic/early stage
  - PMF, overtly fibrotic phase
- **Essential thrombocythemia (ET)**
- Chronic eosinophilic leukemia, not otherwise specified (NOS)
- MPN, unclassifiable

## MPNs & Targeted therapy

- CML was one of the first diseases treated with a targeted therapy – Revolutionized the way CML is treated (and how we think about other diseases).
- Imatinib (Gleevec) was the first compound.
- Now with second and third generation drugs with different side effect profiles.
- Very long-term remissions for many patients and generally well-tolerated.


## Guidelines on when to change TKIs

| | NCCN Guidelines[17] | ELN Recommendations[18] |
|---|---|---|
| Month 3 | • If RT-PCR BCR-ABL > 10% (IS) or Ph positive > 35%, switch therapy, or continue and recheck at 6 months | • If no complete hematologic response and/or Ph positive > 95%, switch therapy<br>• If RT-PCR BCR-ABL > 10% (IS) and/or Ph positive 36% to 95%, retest more frequently |
| Month 6 | • If elected to continue initial therapy, switch therapy if RT-PCR BCR-ABL > 10% (IS) or Ph+ > 35% | • If BCR-ABL > 10%, and/or Ph positive > 35%, switch therapy<br>• If BCR-ABL 1% to 10%, and/or Ph positive 1% to 35%, retest more frequently |
| Month 12 | • If BCR-ABL < 3 log reduction and/or Ph positive > 0, assess with bone marrow cytogenetics<br>• If Ph positive 1% to 35%, may switch or continue therapy<br>• If Ph positive > 35%, switch therapy | • If BCR-ABL > 1%, and/or Ph positive > 0, switch therapy<br>• If BCR-ABL 0.1% to 1%, retest more frequently |
| Month 18 | • If BCR-ABL < 3 log reduction and Ph positive, may need to assess with bone marrow cytogenetics<br>• If Ph positive > 0, switch therapy | |

- More TKIs = more options (and better results).
- If response is suboptimal at certain milestones, there are criteria for switching drugs to improve outcomes.

## Treatment (MPNs)

- Many people with PV, ET, and PMF have a mutation in JAK2
  - Now have drug that targets JAK signaling cascade – ruxolitinib (Jakafi)
  - Main benefit is that it improves the symptom burden/quality of life in patients with myelofibrosis.
- Polycythemia vera (PV)
  - Over-production of red blood cells leads to clot risk, big liver/spleen, itching, vasomotor symptoms, and high blood pressure.
  - May reduce with RBCs by removing blood (phlebotomy) or consider hydroxyurea to suppress the bone marrow. Low-dose aspirin may be used to reduce risk of clotting.

## Treatment (MPNs)

- Essential thrombocythemia (ET)
  - Goals of treatment are to reduce risk of clotting/bleeding and improve symptoms
  - Hydroxyurea and aspirin are the mainstays of therapy. Anagrelide seldom used anymore.
- Primary myelofibrosis
  - Limited options.
  - In low or very-low risk disease, observation is appropriate.
  - In high-risk disease, stem cell transplantation is recommended.

## Summary

- MDS/AML, CMML, and the MPNs are heterogenous diseases that require individualized treatment.
- Treatment plans depend on the disease, the "risk" of the disease, the patient, and their motivation.
- With the exception of ____,* the only curative treatment option is stem cell transplantation.

*** 10 bonus points for the correct answer**

Thank you for your attention!

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