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

Abnormal cells arise as a result of a genetic insult

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

Who is affected

Treatment depends on

- Patient
  - Age
  - Motivation
  - Preference/treatment goals
  - Physical fitness (performance status)
  - Other medical conditions (co-morbidities)
- 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)

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)

- **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.
  - Best supportive care (observation, growth factors, etc)

- **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 trials
  - 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

- **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 approq
  - 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)

**Molecular testing:**
- NPM1
- CEBPA
- FLT3-ITD

**Cytogenetics:**
- WBC at diagnosis:
- Prior chemo/radiation therapy:
- History of preceding MDS

**Method of consolidation depends on risk**

- High WBC at diagnosis
- Prior MDS or chemo/radiation therapy
- 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

**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

**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
- Matched unrelated donor 2011-2012
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

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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 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

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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%

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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

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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
- 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)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Polycythemia vera</td>
<td>Over-production of red blood cells leads to clot risk, big liver/spleen, itching, visominator 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.</td>
</tr>
</tbody>
</table>
| Essential

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### Summary

- MDS/AML, CMML, and the MPNs are heterogeneous 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.*

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Thank you for your attention!

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