Adding insult to injury: MPNs transforming to acute leukemia

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What is acute leukemia?

- Cancer of the white blood cells

- Acute leukemia-
  - Acute myelogenous leukemia
  - Acute myeloid leukemia
  - Myelofibrosis - Blast phase

- Can arise *de novo* or from another bone marrow disorder -- such as MPN - ET/PV/MF

- Rarely, may present as a granulocytic sarcoma/ extramedullary AML
Leukemia Incidence

4% of new cancer cases
44,240 New patients

What do we see?

- Increased blasts in the peripheral blood
- Decrease in normal blood counts
- Increasing fatigue or symptoms

Blast: immature white blood cell
Microscope
I have blasts in my differential?  
Do I have AML?  

NO!!!
What percentage of blasts defines AML?

- For acute myeloid leukemia, also referred to as myelofibrosis - blast phase: >20% blasts

- For myelofibrosis - accelerated phase: 11-19% blasts
How often does this occur?

- **PV**
  - 2.3% at 10 years
  - 5.5% at 15 years
  - <10% at 20 years.

- **ET**
  - 3 per 1000 person-years
  - 2.6% at 10 years
  - 5.3% at 15 years
What increases the risk?

- In PV patients
  - Pipobromman
  - P$_{32}$
  - Busulphan
- In ET patients
  - Little data, but not much seems to contribute to leukemic conversion
How often does MF transform to AML

- In the 525 patients used to develop DIPSS–70 (13%) of patients progressed to blast phase.

- Depending on risks evaluated, can range from 12%-31% at 10 years.
What predicts “blast phase” in PMF

- Increasing WBC, and increased number of blasts in the marrow or peripheral blood
- Platelet count $<100 \times 10^9$
- Increasing number of chromosome mutations in the bone marrow
- Lack of $JAK2/MPL/CAL-R$ mutation
## Myelofibrosis prognosis

<table>
<thead>
<tr>
<th>DIPSS</th>
<th>DIPSS plus</th>
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</thead>
<tbody>
<tr>
<td>Anemia (hgb &lt;10)</td>
<td>DIPSS score</td>
</tr>
<tr>
<td>WBC &gt;25</td>
<td>Platelets &lt;100</td>
</tr>
<tr>
<td>Blasts &gt;1%</td>
<td>Transfusion dependant</td>
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<tr>
<td>Constitutional symptoms</td>
<td>poor risk cytogenetics: complex karyotype or any sole or two abnormalities including +8, -7/7q-, -5/5q-, inv(3), i(17q), 12p-, 11q23 rearrangement</td>
</tr>
<tr>
<td>Age &gt;60</td>
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*Notes:*
- DIPSS: Disease-Independent Prognostic Scoring System
- DIPSS plus: an updated version of DIPSS

*Graphs:*
- Cumulative proportion surviving over time (years) for different DIPSS categories.
- Survival (proportion) over time (months) for different risk groups with statistical significance indicated.

*Additional notes:*
- Myelofibrosis is a bone marrow disorder characterized by fibrosis and replacement of normal bone marrow with fibrous tissue.
- Prognostic factors include anemia, white blood cell count (WBC), platelet count, blast percentage, transfusion dependency, and constitutional symptoms.
- Constitutional symptoms and poor risk cytogenetics (complex karyotype or specific abnormalities) are also important considerations.

*Time points:*
- Intermediate-2: 11.2 years
- Intermediate-1: 7.9 years
- Low: 4 years
- 2.2 years
Chromosome mutations

Prognostically important genes, other than JAK2/CALR/MPL, in essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF)

- SRSF2
- ASXL1
- IDH2
- EZH2
- TP53
- U2AF1
- CBL
- SF3B1
- SH2B3
How do we treat blast phase?

- Hypomethylating agents:
  - 5-azacitadine or decitabine
  - Sometimes can add another agent on in the setting of a clinical trial

- Induction chemotherapy $\Rightarrow$ bone marrow transplant

- Targeted agents on clinical trial: such as IDH1 or IDH2 inhibitor, spliceosome inhibitor, Flt-3 ITD inhibitor
Hypomethylating agents

- Outpatient chemotherapy
- Given 5-7 days as either IV infusion or subcutaneous injection
- Well tolerated, may cause a little nausea, but no hair loss.
- Do not cure disease, help slow down the pace
Induction chemotherapy

- **Induction**: “7 + 3”
  - Cytarabine (ARA-C) 100 mg/m²/day continuous infusion x 7 days
  - Anthracycline on days 1-3
  - Goal: get rid of leukemia!

- Response assessment:
  - Difficult in MF due to abnormal marrow at baseline
  - Often determined by blasts in the blood/count recovery
Bone marrow transplant!

- Unlikely to stay in remission with induction chemotherapy alone

- Bone marrow transplant can help maintain the remission
Induction chemotherapy
bone marrow transplant

- Significant morbidity and mortality

- Limited to patients who are young and/or fit enough to tolerate treatment
Targeted therapies: AML is a complex biological disease

Chromatin modifiers (30.5%)
- MLL fusions, MLL PTD, NUP98-NSD1, ASXL1, EZ112, KDM6A, other modifiers

Myeloid transcription factors (22%)
- RUNX1, CEBPA, other myeloid transcription factors

Tumor suppressors (16.5%)
- TP53, WT1, PHF6

Cohesin complex (13%)

Activated signaling (59%)
- FLT3, KIT, KRAS, NRAS, PTPs, Ser/Thr kinases, other Tyr kinases

Spliceosome (13.5%)

Transcription factor fusions (18%)
- PML-RARA, MYH11-CBF, RUNX1-RUNX1T1, PICALM-MLLT10

NPM1 (27%)

DNA methylation (46%)
- TET1, TET2, IDH1, IDH2, DNMT3B, DNMT1, DNMT3A

An ounce of prevention is worth a pound of cure

-Benjamin Franklin
Understand risk factors associated with your disease

- If you fall into a high risk group-
  - Peripheral blood blast percentage
  - Abnormal chromosomes on bone marrow biopsy
  - Mutations associated with higher risk disease

- Consider earlier treatment
  - Bone marrow transplant
  - Hypomethylating agent (in the case of increased blasts)
Summary

- Acute myeloid leukemia, or MF-blast phase is a serious complication of MPN

- Understanding the risk factors will help decide frequency of monitoring and treatment strategies

- There are treatments available, however, important to establish goals of care up front