Adding insult to injury: MPNs transforming to acute leukemia

Jeanne Palmer

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Mayo Clinic, Phoenix, AZ

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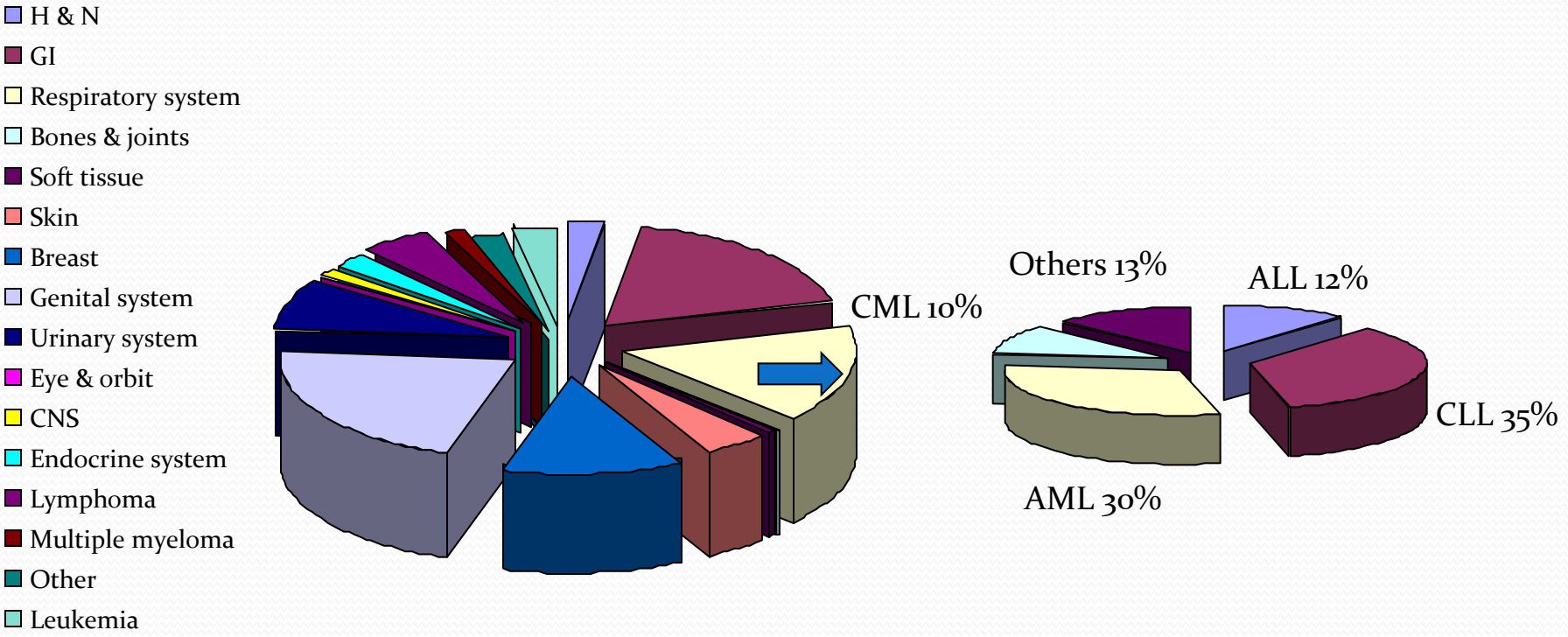
What is acute leukemia?

- 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

Jemal, A. et al. CA Cancer J Clin 2007

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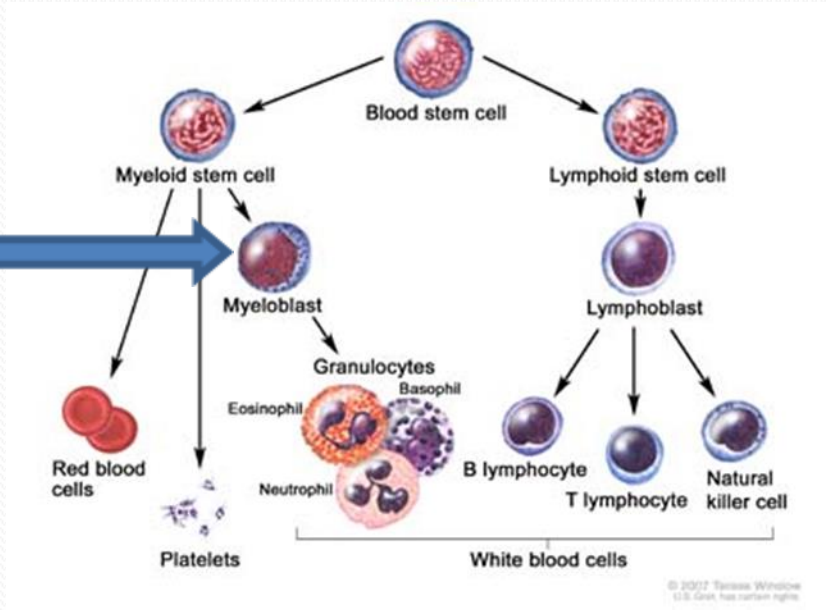
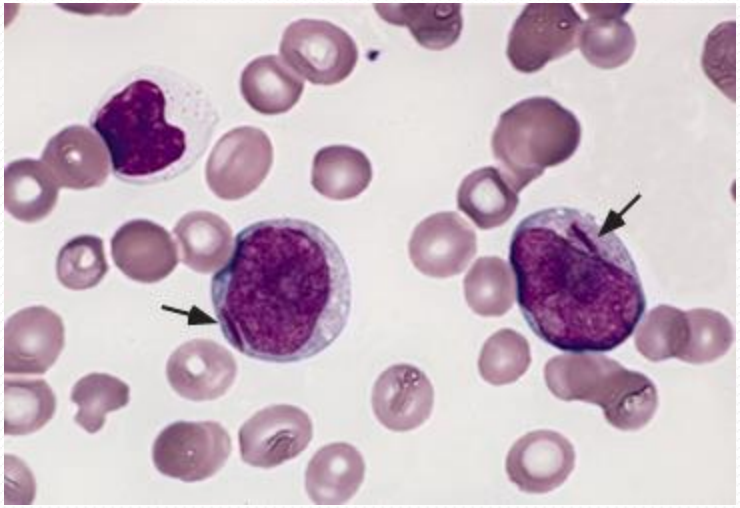
What do we see?

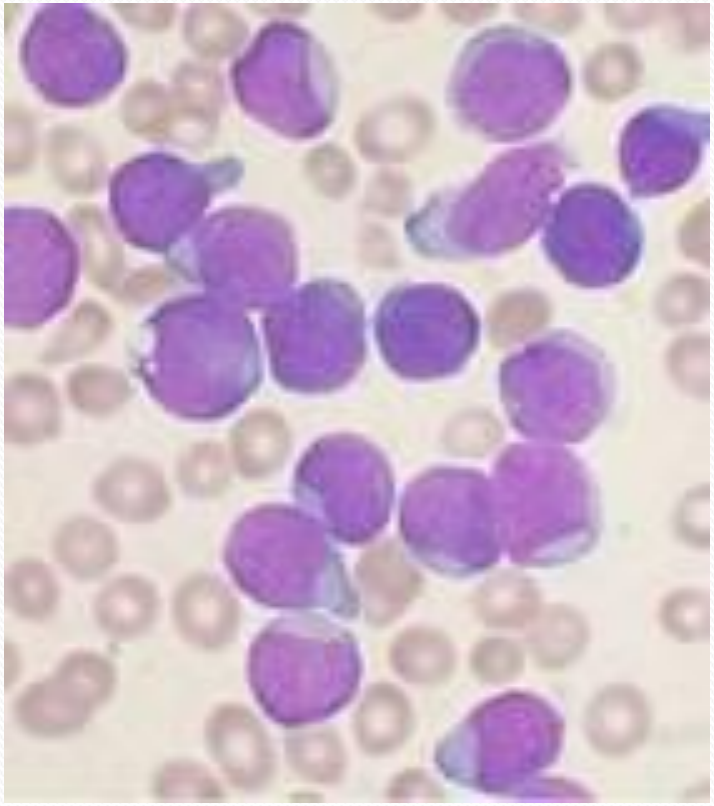
- Increased blasts in the peripheral blood
- Decrease in normal blood counts
- Increasing fatigue or symptoms

Blast: immature white blood cell



Microscope





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I have blasts in my differential? Do I have AML?

NO!!!

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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
  - Pipobroman
  - P^{32}
  - Busulphan
- In ET patients
  - Little data, but not much seems to contribute to leukemic conversion

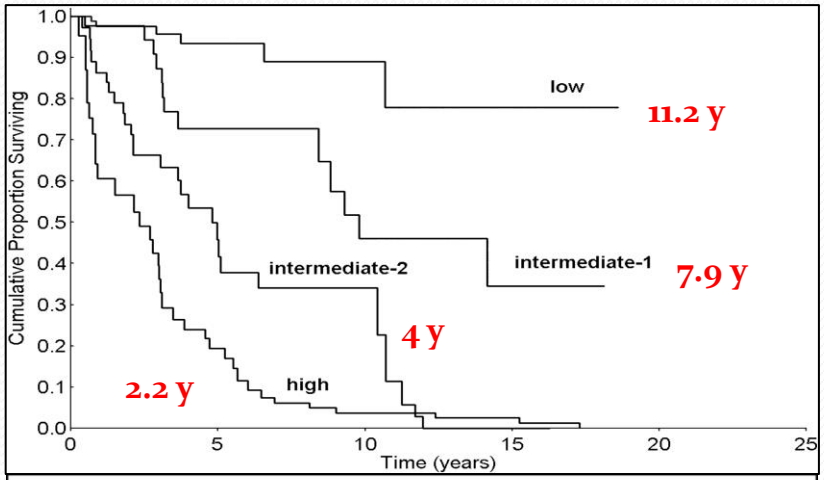
How often does MF transform to AML

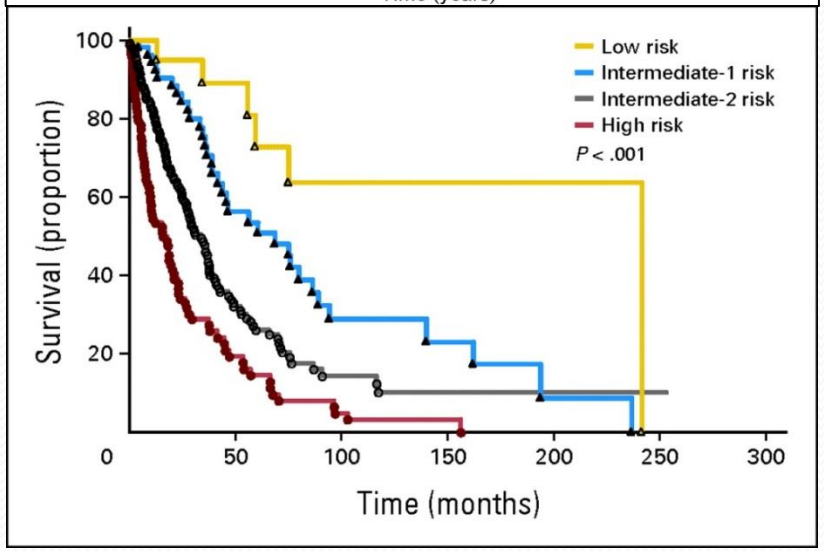
- In the 525 patients used to develop DIPSS– 70 (13%) of patients progressed to blast phase
- Depending on risks evaluated, can range from 12%-31% at 10 years

What predicts “blast phase” in PMF

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

Myelofibrosis prognosis





DIPSS	DIPSS plus
Anemia (hgb <10)	DIPSS score
WBC >25	Platelets <100
Blasts >1%	Transfusion dependant
Constitutional symptoms	poor risk cytogenetics: complex karyotype or any sole or two abnormalities including +8, -7/7q-, -5/5q-, inv(3), i(17q), 12p-, 11q23 rearrangement
Age >60	

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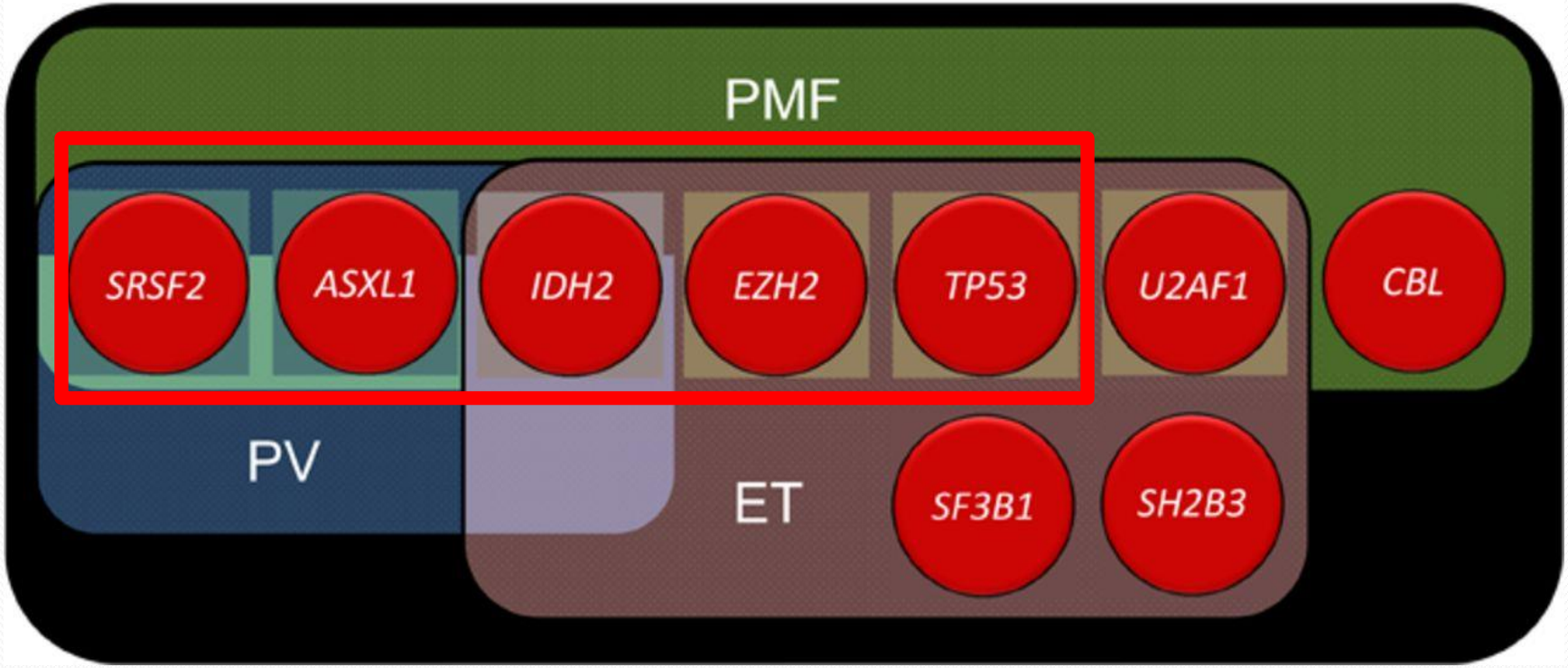
Chromosome mutations

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



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 ➡ 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

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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

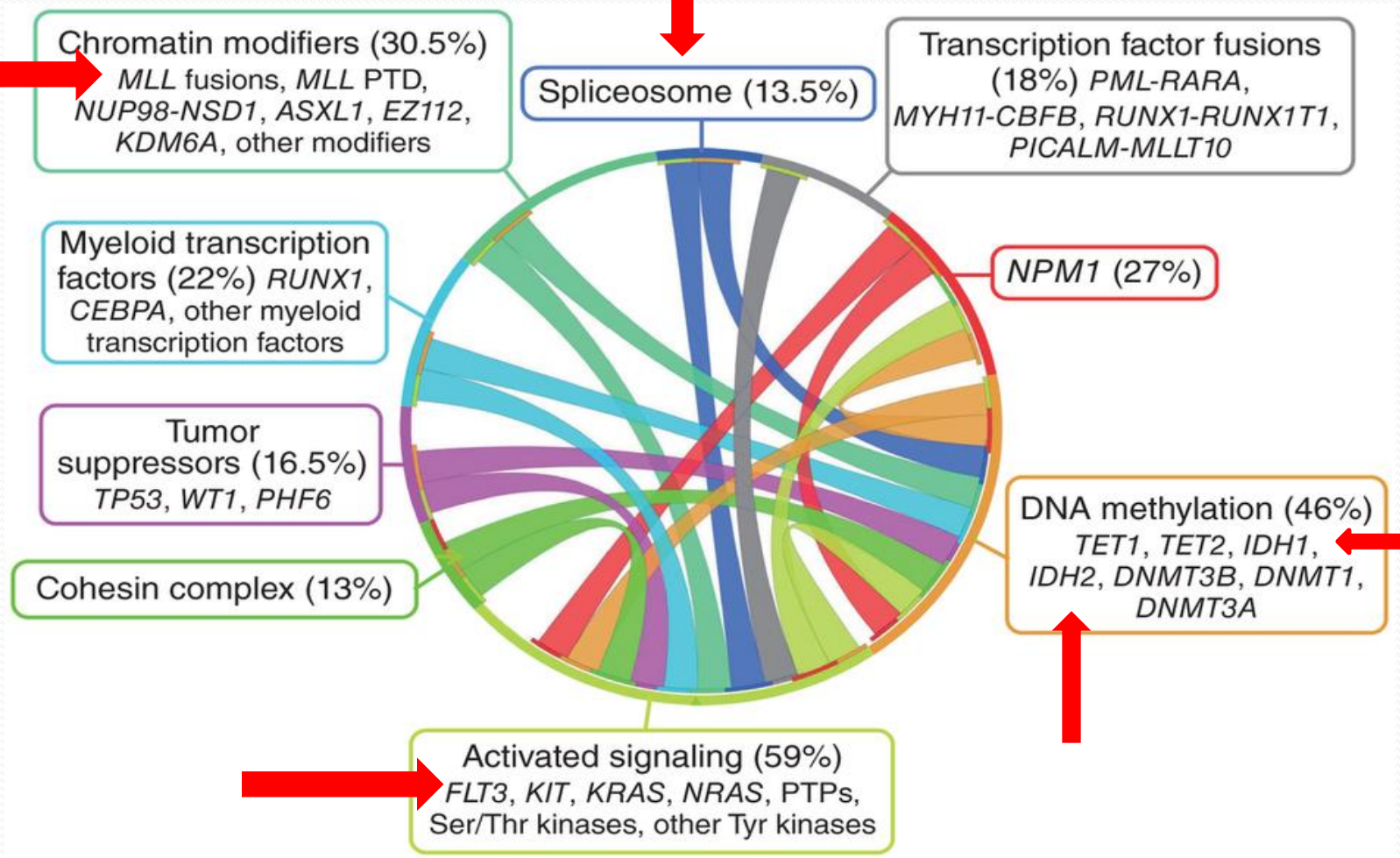
Bone marrow transplant!

- 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



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Sai-Juan Chen et al,Nature Genetics 2013; 45,586–587.

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