MYELOPROLIFERATIVE NEOPLASMS

Jonathan Abbas, MD

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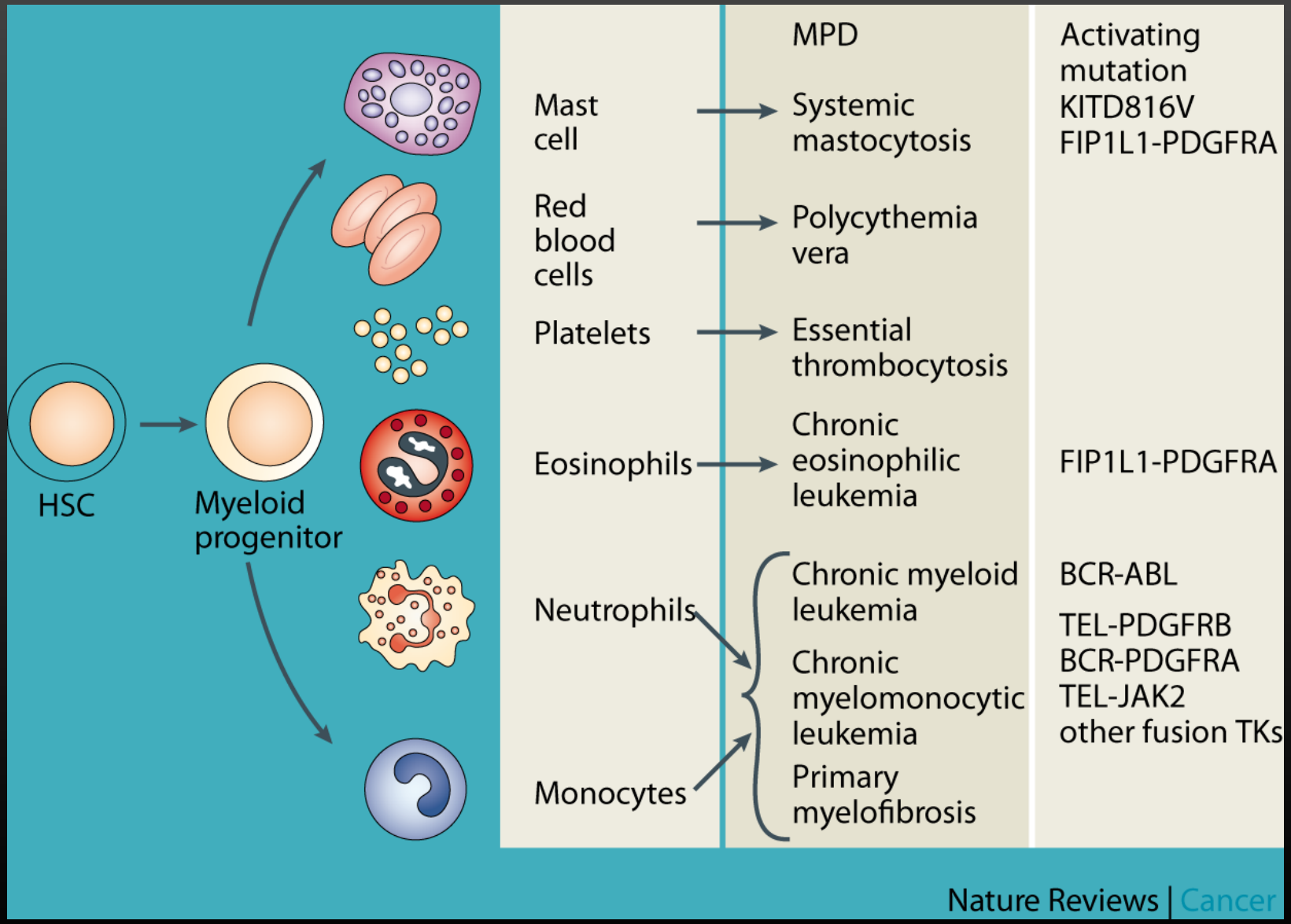
Myeloproliferative Disorders



Overview

- Chronic Myeloid Leukemia
- Polycythemia Vera
- Essential Thrombocytosis
- Primary Myelofibrosis

MPNs

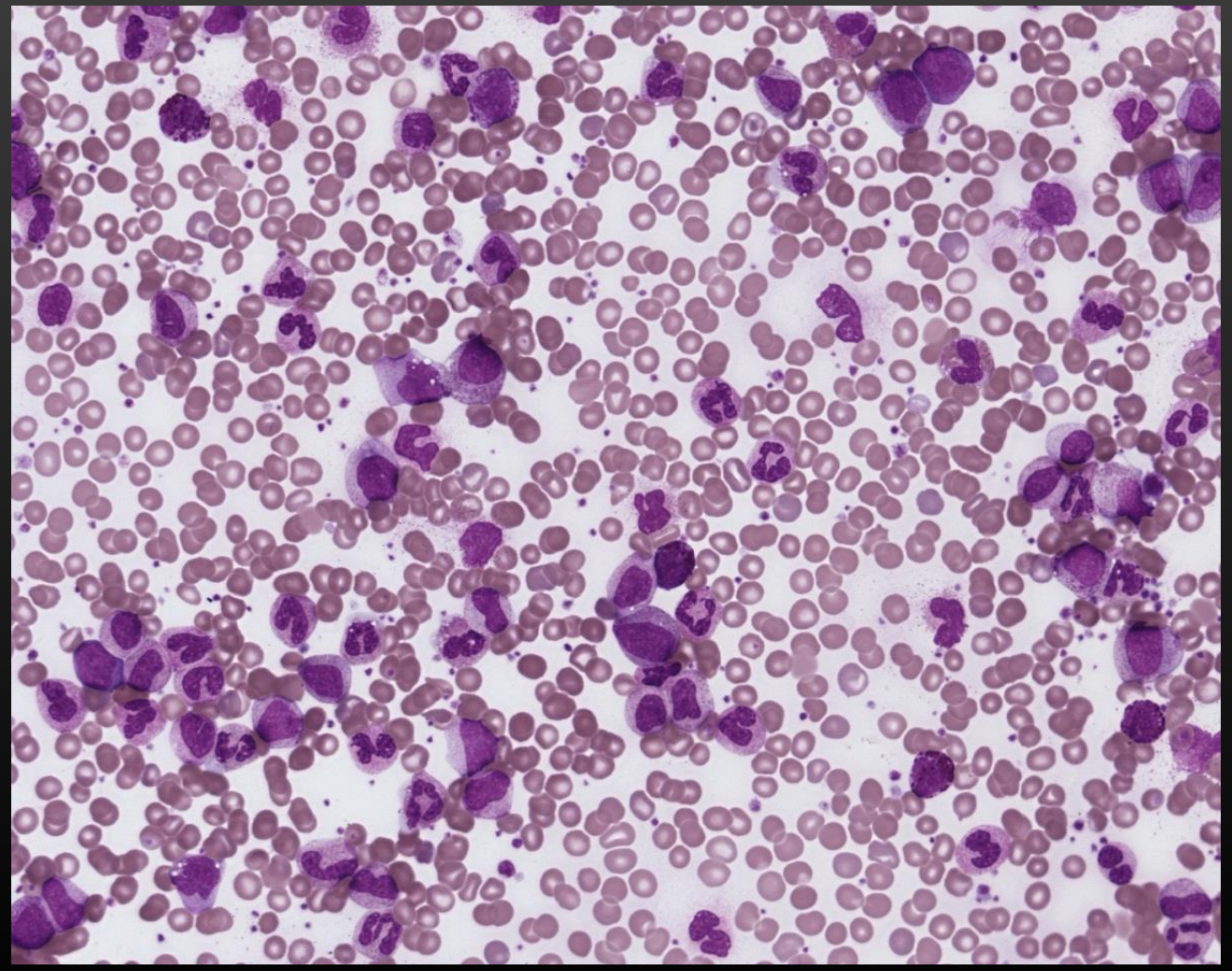
Ph +	Ph -
CML	PV
	ET
	PMF

Chronic Myeloid Leukemia

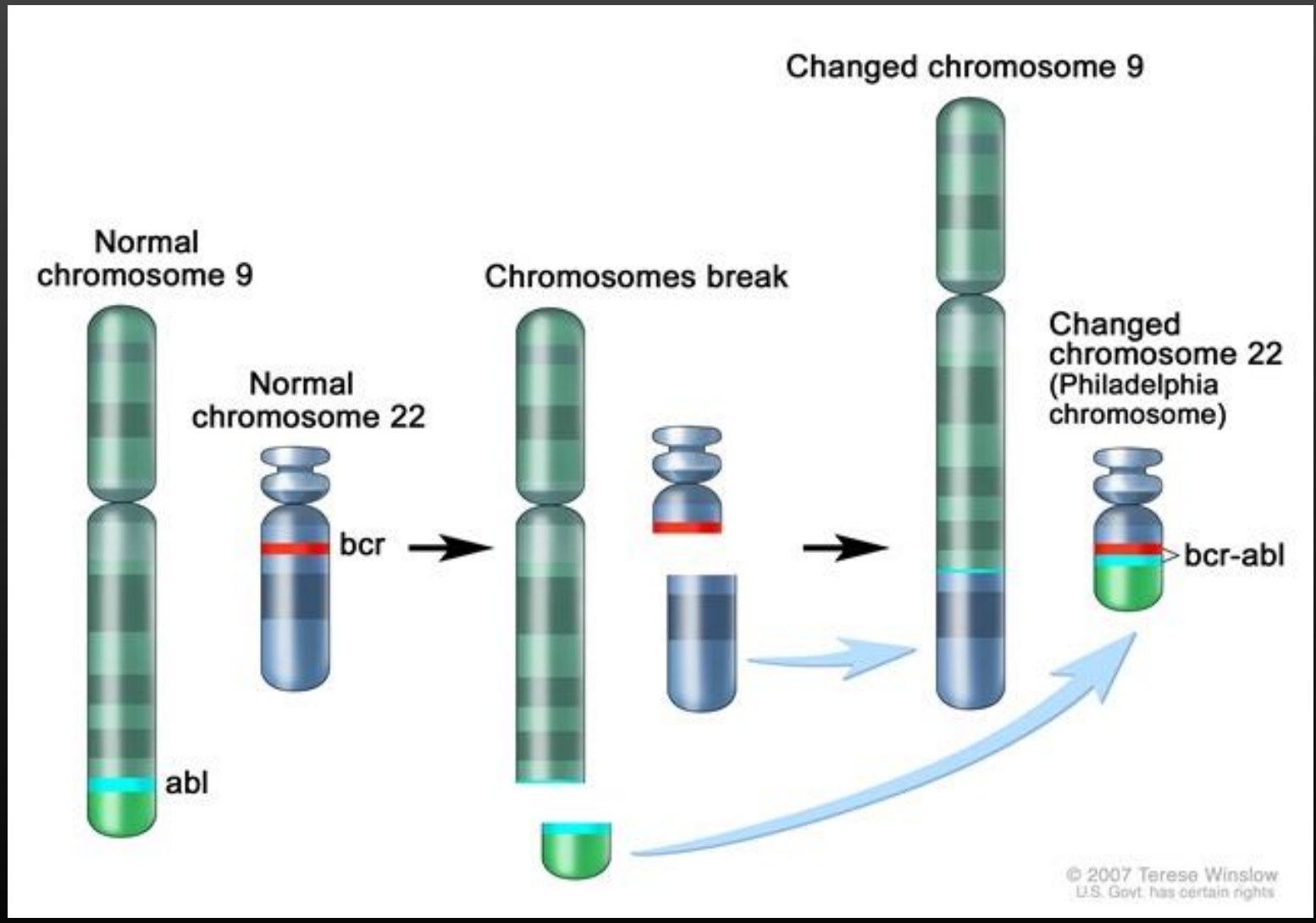
- 6000 new cases in 2013
- 15% of adult leukemias
- Median age 67
- Seen in all age groups
- Defined by BCR-ABL t(9;22) Philadelphia chromosome

Morphology

- No leukemic arrest
- Accompanying eosinophilia and basophilia



Philadelphia Chromosome



CML Clinical Presentation

A 36 year old man presents to the ER with 1 week of mild L sided abdominal pain more uncomfortable after eating. He has had a 5# weight loss and mild fatigue over the past few months.

CBC reveals a WBC of 248,000u/L, Hgb 9.4g/dL, Plts 360u/L

Differential is 60% neutrophils, 22% lymphocytes, 8% monocytes, 6% basophils, 4% eosinophils. No blasts are noted in peripheral blood smear review

On exam he has marked splenomegaly but no other findings. All other labs including CMP, uric acid, and DIC panel are normal

Question 1: CML Presentation

Next step in management of this patient is:

A. Outpatient referral to hematologist for further workup

B. Admission to hospitalist service for emergent leukopheresis

C. Admission to hospitalist service for treatment with hydroxyurea

D. Packed RBC transfusion for a Hgb of 9.4g/dL

The clinical presentation of CML can be benign, and workup does not always require admission and emergent management

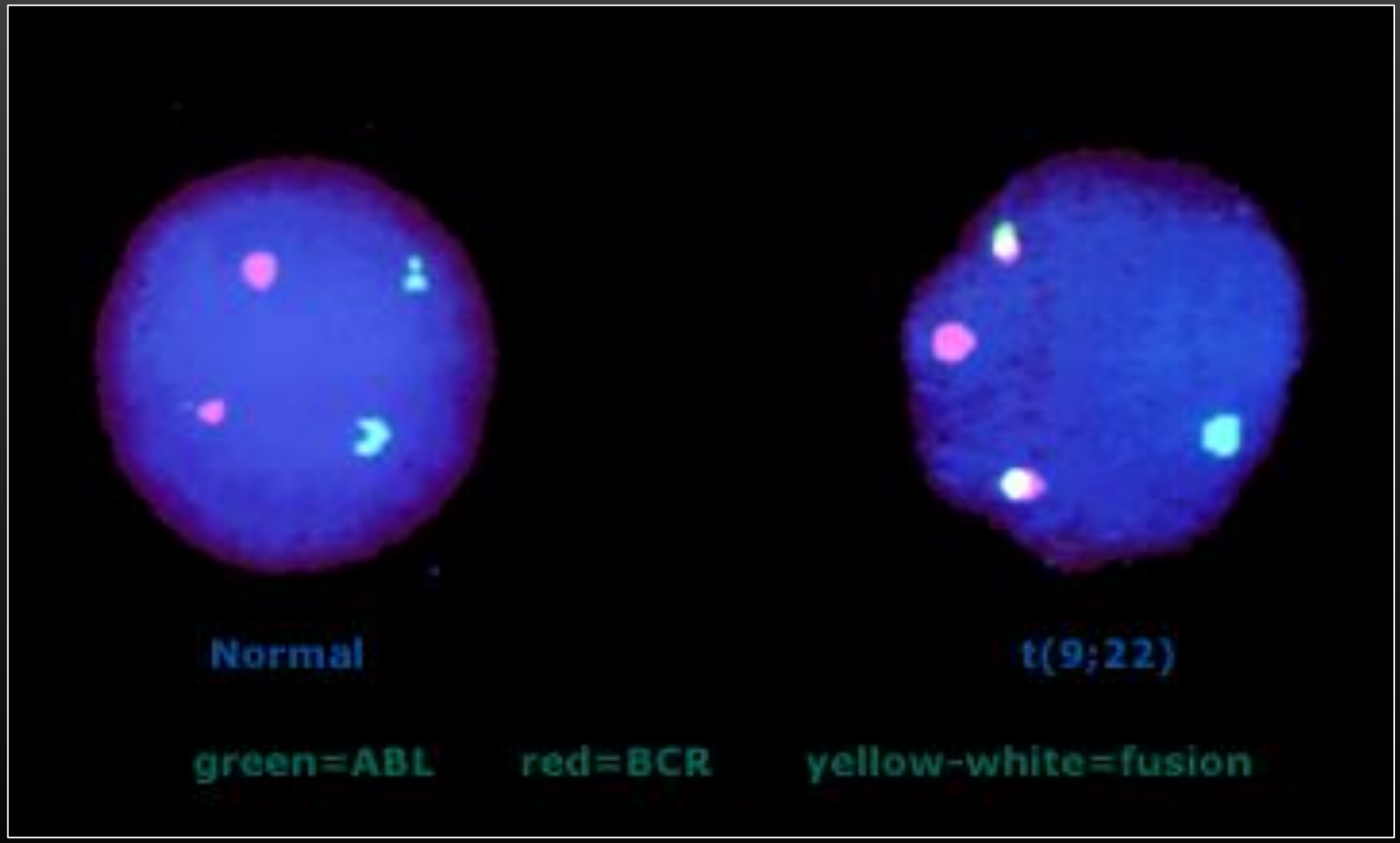
CML Workup

Very high clinical suspicion based on CBCd and peripheral blood smear alone

Bone Marrow Biopsy

- Baseline for further assessments
- Assess percentage of blasts to define the phase of CML
- Confirm presence of Philadelphia chromosome
- Test for additional cytogenetic abnormalities

CML Diagnosis by FISH for t(9;22)



CML Phases

Chronic Phase

- Most common presentation
- Usually found incidentally on CBC
- Will progress to Accelerated or Blast Phase in 3-5 years if untreated

Accelerated Phase

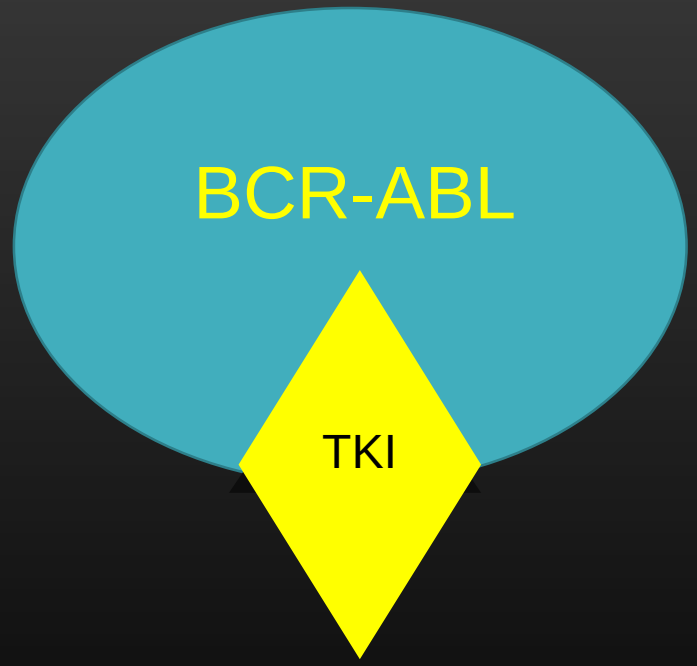
- 10-19% blasts

Blast Phase

- > 20% blasts
- Treated like an acute leukemia (may be myeloid or lymphoid blast crisis)

CML Treatment

Tyrosine Kinase Inhibitors (TKIs) have revolutionized CML treatment



BCR-ABL is the
leukemia ON switch

TKI inhibits BCL-ABL,
turning OFF the ON switch

CML Treatment

Chronic Phase Treatment

- TKI therapy provides durable remission
- *BCR-ABL* PCR < 10% at 3 months is the major predictor of survival

- Imatinib (Gleevec): 1st generation TKI
  - Side effects: fluid retention, nausea, vomiting, diarrhea
- Nilotinib (Tasigna): 2nd generation TKI
  - Side effects: QT prolongation, arrhythmias
- Dasatinib (Sprycel): 2nd generation TKI
  - Side effects: cough, pleural effusions

CML Frontline Treatment

Advantages of Nilotinib (2nd gen) vs Imatinib (1st gen)

ENESTnd Study

- Nilotinib at 300mg BID or 400mg BID vs Imatinib at 400mg BID
- Deeper molecular responses
- Fewer progressions to AP/BC on therapy (1% vs 6%)

CML duration of therapy

Until recently, TKIs were considered lifelong treatments

ENESTop Study

- Must have been on nilotinib for at least 2 years with a major molecular response (log $^{-4.5}$)
- Take 1 additional year of nilotinib, maintaining MMR
- Discontinue treatment
- 50% remained in remission after discontinuation
- 50% progressed, but regained deep remission when restarting nilotinib

3rd generation TKIs

Reserved for failure of 1st and 2nd generation TKIs

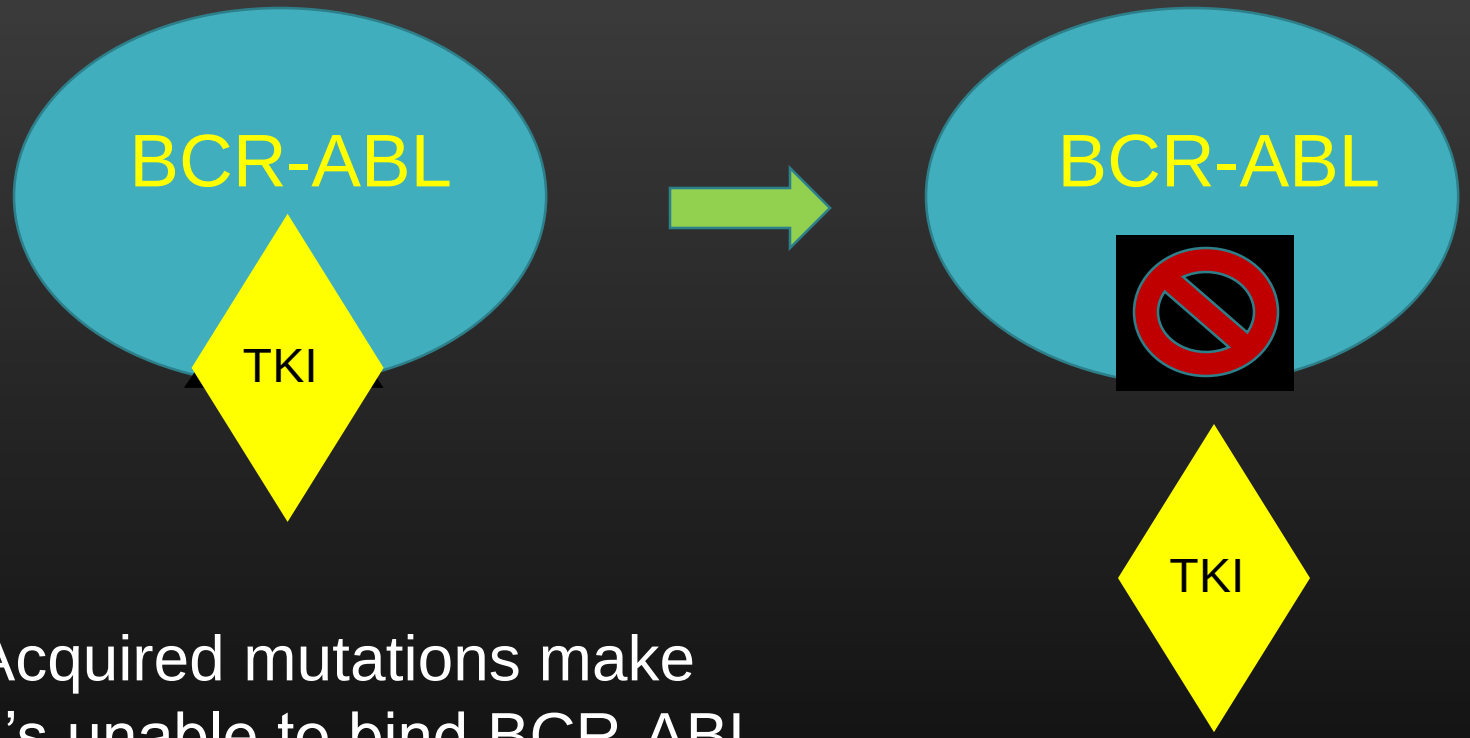
Bosutinib (Bosulif)

- Side effect: diarrhea

Ponatinib (Inclusig)

- Most potent TKI
- Black box warning for arterial and venous thrombosis
- Initial FDA approved dose of 45mg rarely used, now far safer at 30mg or 15mg

CML: Why TKI's stop working



Acquired mutations make
TKI's unable to bind BCR-ABL

Only Ponatinib works if
there is a T315I mutation

Question 2: CML Chronic Phase treatment

A 45 year old with newly diagnosed Chronic Phase CML has been on Imatinib for 3 months. His BCR-ABL PCR was 94% on admission, and at 3 month recheck is down to 56%. The next step in management is:

A. Increase the dose of imatinib

B. Switch to a second generation TKI such as nilotinib or dasatinib

C. Test for ABL Kinase mutation

D. B and C

BCR ABL > 10% after 3 months of therapy his highly predictive of treatment failure and progression. Therapy should be escalated and ABL kinase mutation testing should be sent

Question 3: CML Treatment failure

The most common cause of TKI failure is:

A. Acquired ABL mutations leading to resistance

B. Intolerance to the side effects of TKIs

C. Progression to accelerated or blast phase

D. Patient noncompliance

TKI therapy is highly effective and thus failures are rare. Medication compliance should be reinforced at every visit.

CML Treatment

Accelerated Phase Treatment

- TKI therapy alone can return to Chronic Phase

Blast Phase Treatment

- Found on initial presentation or progressed from chronic phase
- Despite being a myeloid leukemia, 40% of Blast Phases are lymphoid blasts
- Induction chemotherapy + TKI
  - Myeloid blast phase: Treat like AML
  - Lymphoid blast phase: Treat like ALL
- Relapse certain without allogeneic stem cell transplant

CML: Stem Cell Transplant

TKIs provide durable remissions and have made transplant for CML rare

Indications for Allogeneic Stem Cell Transplant in CML

- Presents in Blast Phase
- Failure to convert Accelerated Phase to Chronic Phase with TKI
- Fails TKI Therapy
  - Acquired mutations making TKIs ineffective
  - Intolerance

Question 4: CML drug toxicity

A 67 year old with a history of COPD and total right pneumonectomy for NSCLC is diagnosed with Chronic Phase CML. Based on his comorbidities which drug would be a poor choice of therapy?

A. Ponatinib

B. Dasatinib

C. Nilotinib

D. Bosutinib

Dasatinib has the most pulmonary side effects of any TKI including cough, pneumonitis, and pleural effusions

Question 5: CML drug toxicity

A 42 year old with a history of antiphospholipid antibody syndrome and a history of a stroke is diagnosed with Chronic Phase CML. Based on these comorbidities which is a poor choice of therapy?

A. Ponatinib

B. Dasatinib

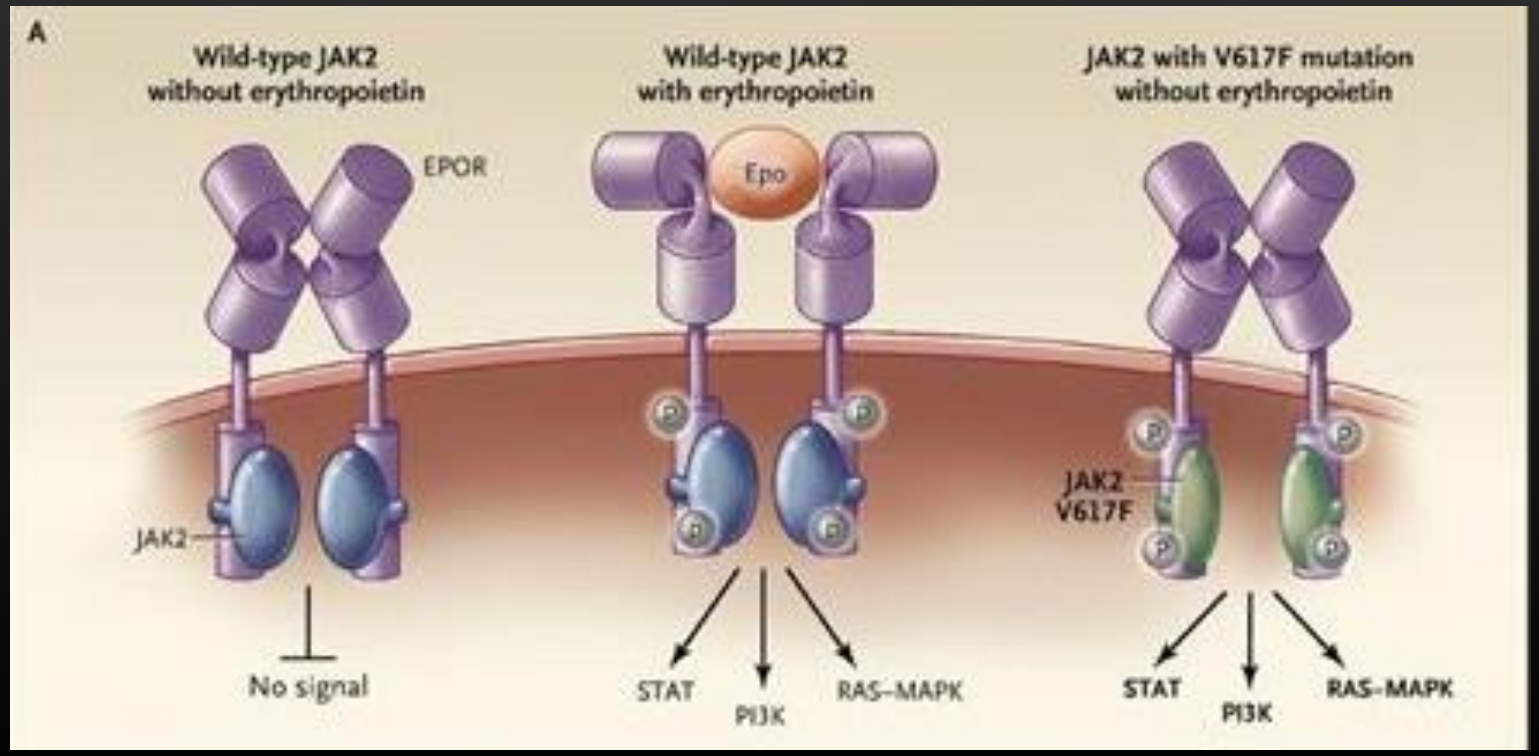
C. Nilotinib

D. Bosutinib

Ponatinib carries a risk of arterial and venous thrombosis and would be contraindicated in this patient

Polycythemia Vera

- MPN characterized by increased proliferation of erythroid, megakaryocyte, and granulocyte precursors
- Most clinical signs seen due to high RBC production
- Defined by the V617F JAK2 mutation (95% of PV)
- Average age 63
- Most patients live a normal lifespan



Question 6: PV Presentation

A 68 year old man presents to his PCP with L sided abdominal pain and flushing that is worse after showering. A CBC reveals a Hgb of 19. EPO level is low at 5

The next step in management is:

A. Referral to a hematologist for a bone marrow biopsy

B. Admission for emergent phlebotomy

C. Begin Erythropoietin injections

D. Check for a JAK2 mutation in peripheral blood

Polycythemia Vera is often partially worked up by PCPs before hematology referrals are made

PV Diagnostic Criteria

Defined with 3 major or first 2 major and minor

Major Criteria

- Hgb > 16.5g/dL in men or 16g/dL in women
- BM morphology showing hypercellularity with trilineage hyperproliferation
- JAK2 mutation positive

Minor criteria

- Low EPO level

PV Treatment

Goals of therapy: Reduce thrombotic risk and vasomotor symptoms

Aspirin

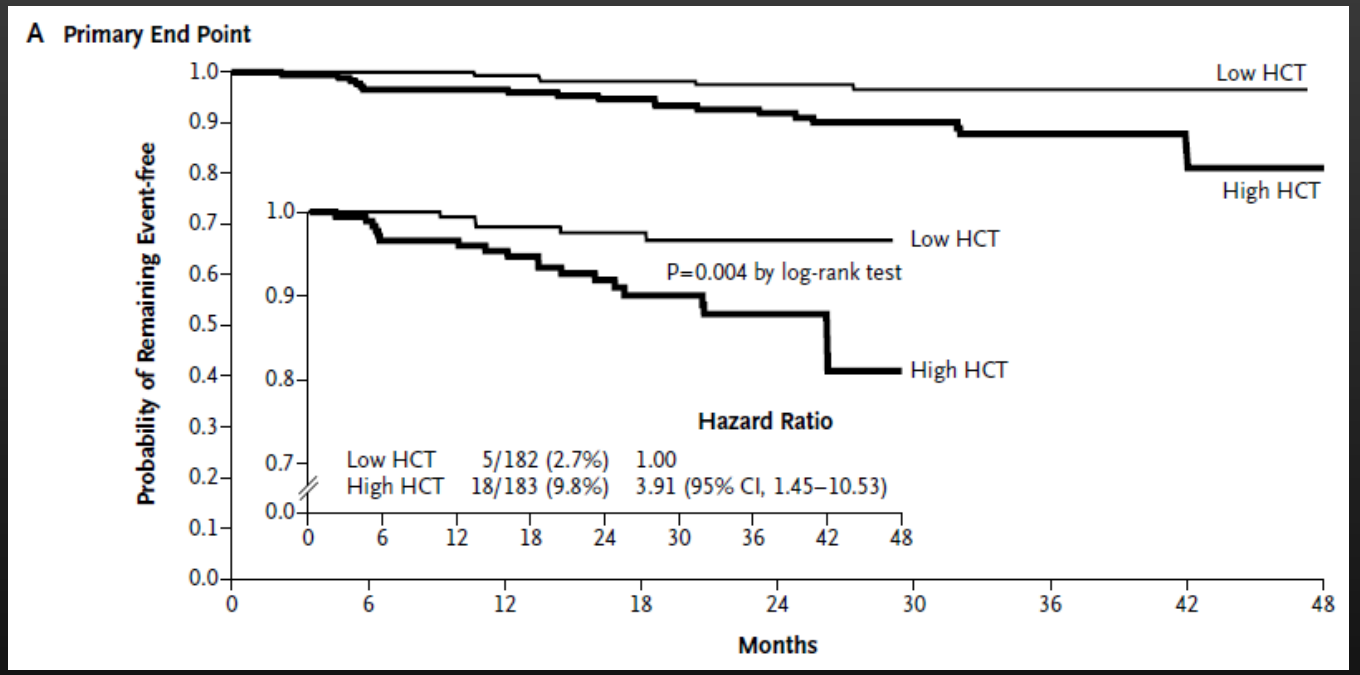
Reduces thrombotic risk and vasomotor symptoms

Phlebotomy

Goal is to maintain Hct < 45%

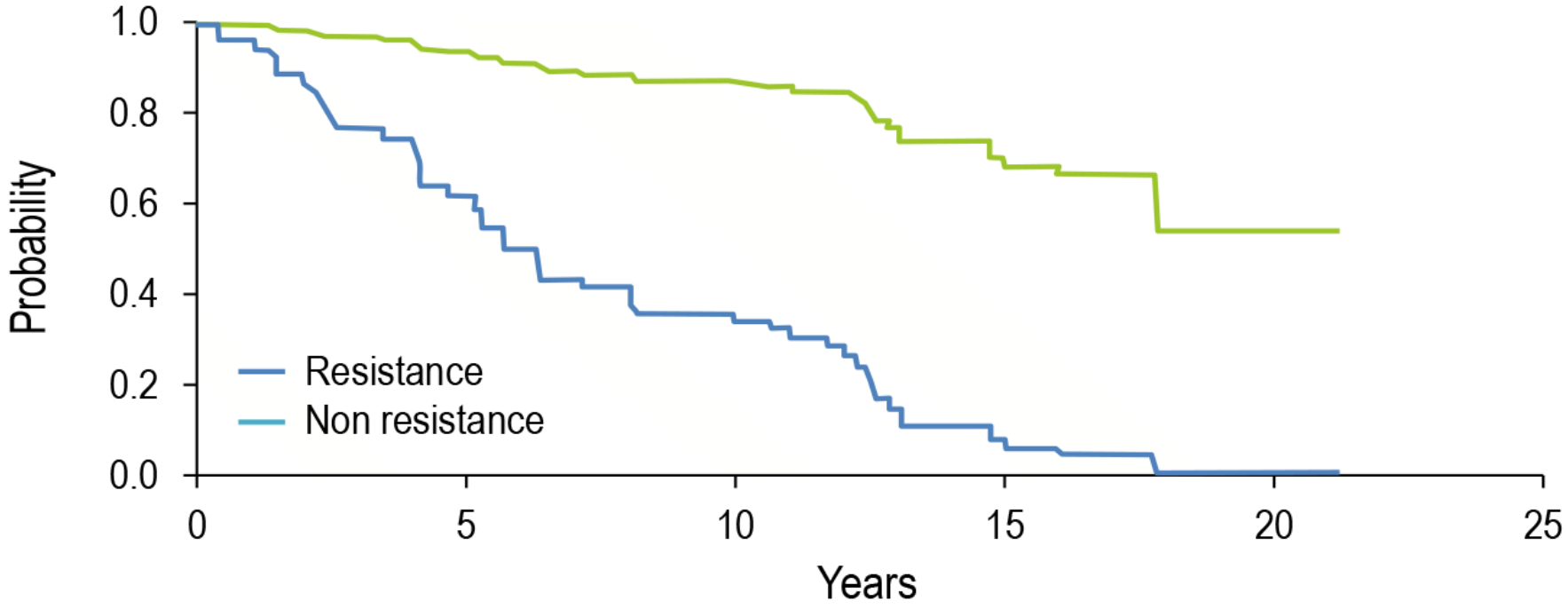
Hydroxyurea

Often used to supplement phlebotomy or when phlebotomy becoming more frequent



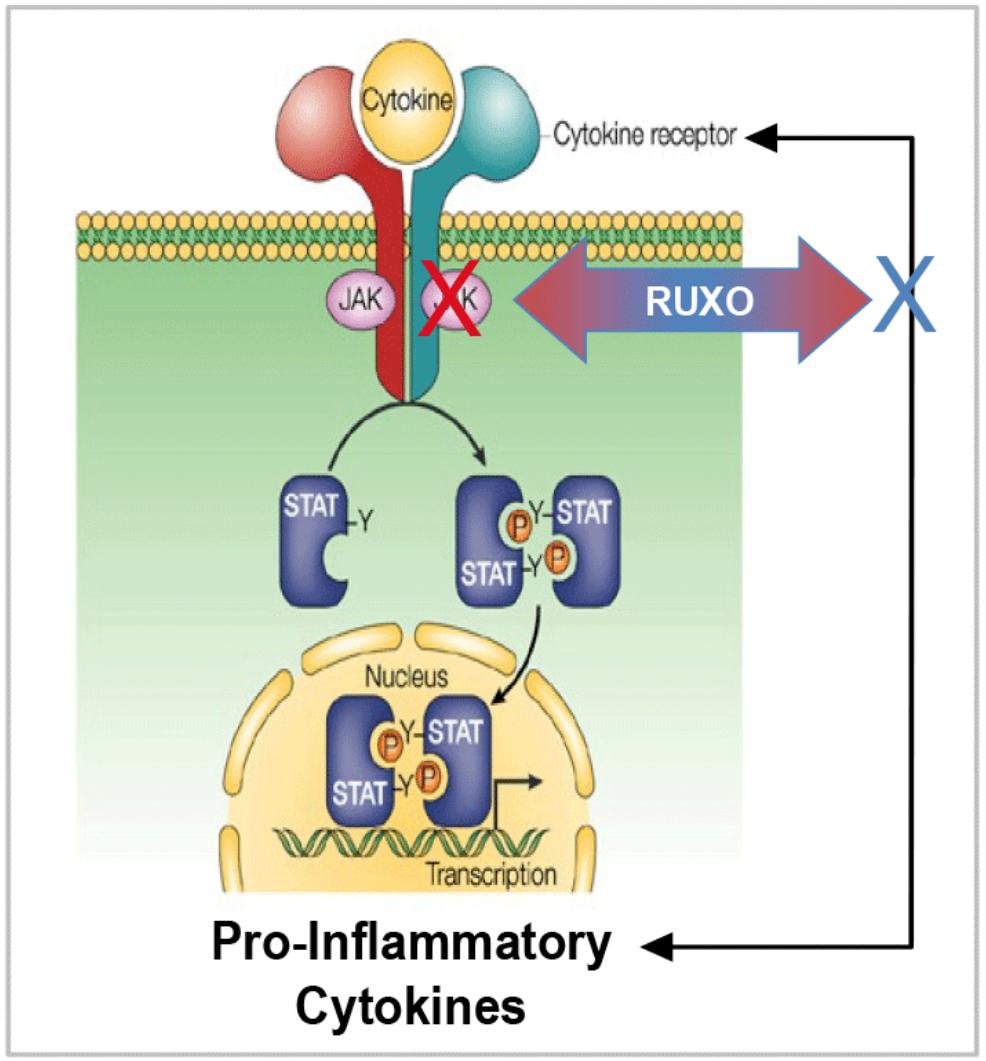
Targeting Hct 45% vs 50% reduces thrombotic risk

Hydroxyurea Resistance



- Resistance to hydroxyurea was associated with higher risk of:
  - Death (HR, 5.6; 95% CI, 2.7%-11.9%; P < .001)

Ruxolitinib (Jakafi)



Inhibitor of JAK2 approved for PV that is refractory to phlebotomy and hydrea

RESPONSE Trial: Ruxolitinib vs BAT

- Spleen size reduction
- Improved Hct
- Improved QOL

Essential Thrombocytosis

- MPN characterized by increased proliferation of megakaryocytes without erythroid or neutrophil proliferation
- Clinical symptoms related to high platelet count
- 50-60% have JAK2 mutation, CALR and MPL mutations may be present
- Average age 55 yo, may present in teens
- Rarest of MPNs
- Longest life expectancy

Question 7: ET Presentation

A 23 year old HIV positive man is admitted to the ICU for sepsis. WBC is 18,000u/L, Hgb 14.4g/dL, and platelets 520,000u/L. Blood cultures are positive for *Pseudomonas aeruginosa.* After antibiotics and supportive care he is discharged home with follow up to his PCP in a week.

The next step in management is:

A. JAK2 mutation testing

B. Hematology referral for bone marrow biopsy

C. Repeat a CBC

D. Initiate therapy with Ruxolitinib (Jakafi)

Causes of reactive thrombocytosis should be ruled out before entertaining a diagnosis of ET

ET Diagnostic Criteria

Defined with 4 major or first 3 major and minor

Major Criteria

- Plt > 450
- BM morphology showing megakaryocyte hyperproliferation without erythroid or granulocytic proliferation
- Not meeting criteria for CML, PV, MF, or MDS
- JAK2, CALR, or MPL mutation

Minor criteria

- No evidence of reactive thrombocytosis

ET treatment

Goal: Reduce vasomotor symptoms, decrease bleeding risk, decrease thrombotic risk

Aspirin

81mg daily or BID usually controls vasomotor symptoms

Bleeding Risk

Platelet counts > 1,000,000 are an *increased* risk of bleeding

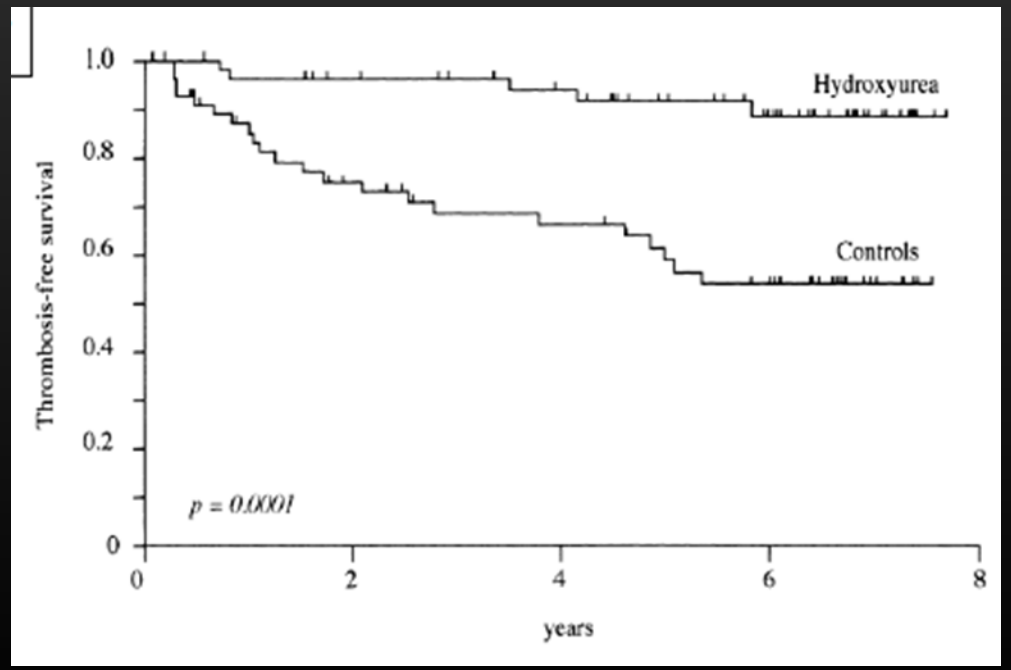
Platelet aggregation causes VWF sequestration leaving inadequate VWF for platelet adhesion

ET treatment

Hydroxyurea

Cytoreduction decreases clotting risk in high risk patients

Patients > 60 with history of thrombosis randomized to hydroxyurea vs placebo



	Age <60yo	Age >60yo
No prior Thrombosis	NO CYTOREDUCTION	Cytoreduce
Prior Thrombosis	Cytoreduce	Cytoreduce

Primary Myelofibrosis

MPN characterized by hyperproliferation of marrow with *secondary* collagen fibrosis and resulting cytopenias

50% of patients have JAK2 mutations, and other mutations may be present

Median age at diagnosis 65

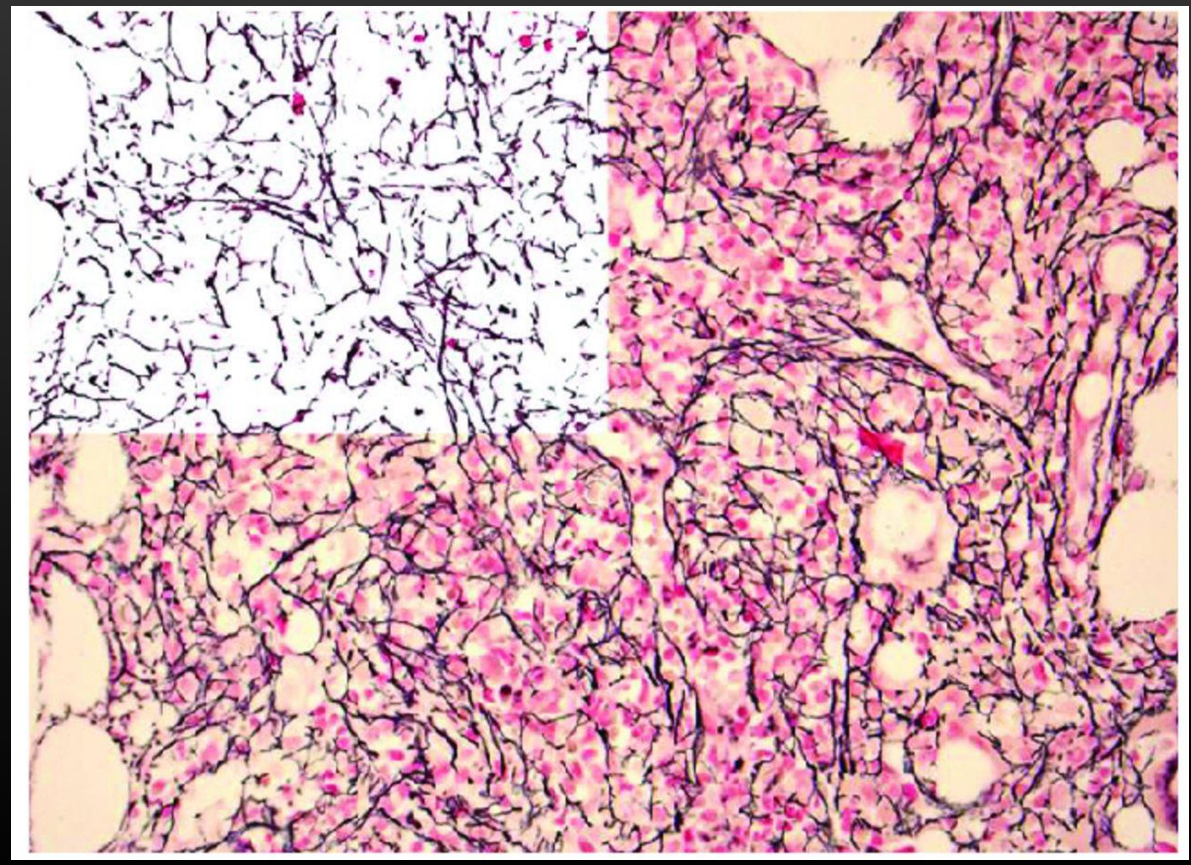
Clinical presentation includes pruritis, bone pain, splenomegaly, anorexia, cytopenias

Variable life expectancy from median 2 to 11 years, based on risk of transformation to acute myeloid leukemia (AML)

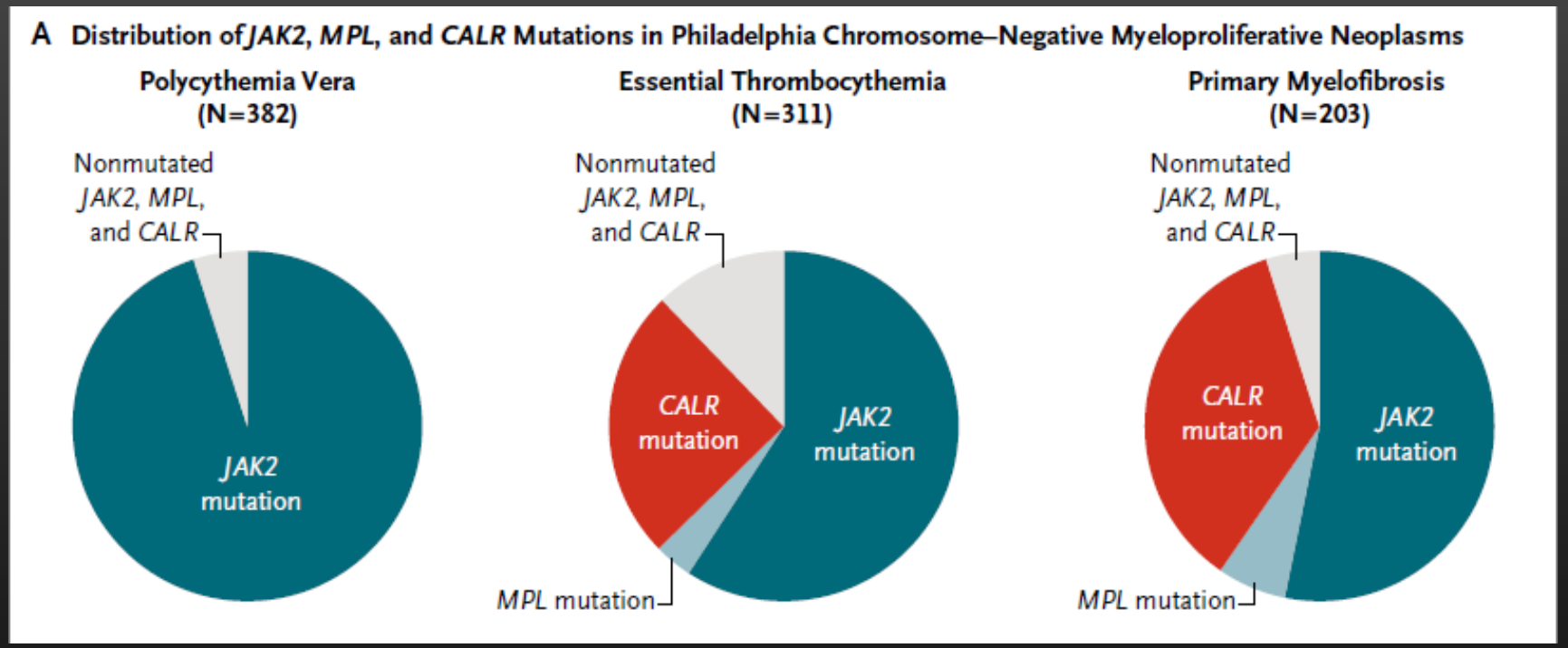
Myelofibrosis presentation

65 year old man presents to ER with 6 weeks of progressive weight loss and new onset abdominal pain. CT scan shows massive splenomegaly and inflamed diverticuli. CBC shows WBC 2,400u/L, ANC 800u/L, Hgb 7.8g/dL, Plts 110,000u/L

While being treated inpatient for diverticulitis a hematology consult is obtained, and a BM biopsy reveals the following



Additional mutations in MPNs



Myelofibrosis Prognosis by Mutation

- CALR mutation: Median survival 17.5 years
- “Triple Negative”: Median survival 1.2 years (high risk AML transformation)

Myelofibrosis treatment

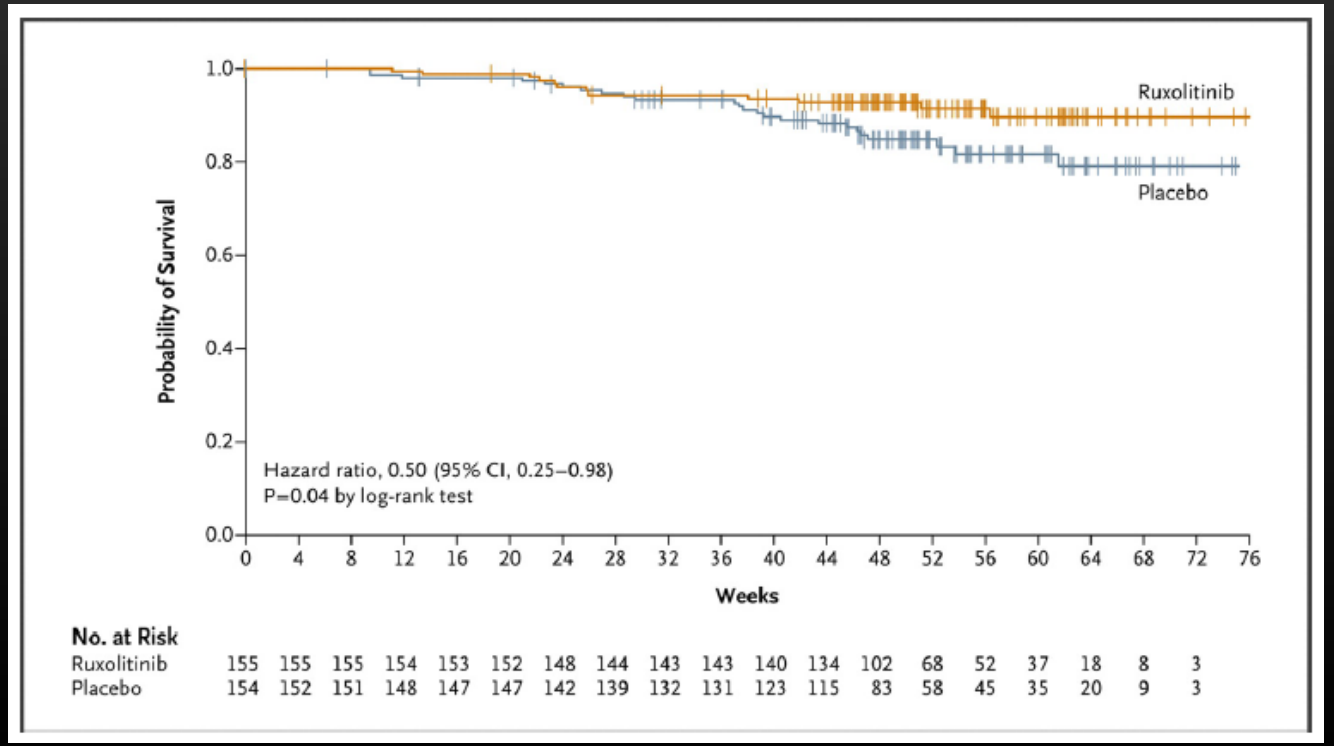
COMFORT I and II trials

Ruxolitinib vs Placebo and Ruxolitinib vs BAT

Endpoints of reduction in spleen size, improvement in cytopenias, and QOL were met

COMFORT I long term follow up showed overall survival advantage for Ruxolitinib

Implies modifying disease course, not merely improving symptoms



Myelofibrosis treatment: Fedratinib

Second JAK2 inhibitor approved for Myelofibrosis in August 2019

JAKARTA 2 Study

- 97 patients with myelofibrosis resistant to or intolerant to Ruxolitinib
- 55% reduction in spleen size

Question 7: Myelofibrosis Management

An asymptomatic 56 year old is found to be mildly pancytopenic with palpable splenomegaly on exam. A bone marrow biopsy confirms myelofibrosis. Mutation analysis reveals no mutations of JAK2, MPL, and CALR

Which statement is true regarding treatment options:

A. “Triple Negative” myelofibrosis in a minimally symptomatic patient carries a favorable prognosis and can be observed off therapy for years

A. Ruxolitinib will be ineffective in “Triple Negative” myelofibrosis

C. Fedratinib is approved for “Triple Negative” myelofibrosis

D. “Triple Negative” myelofibrosis carries a poor prognosis and the patient should be referred for stem cell transplant evaluation

MF lacking JAK2, MPL, and CALR mutations has a high risk of AML transformation and a median survival of just over a year

Question 8: Myelofibrosis Management

A 67 year old is found to be pancytopenic with weight loss and massive splenomegaly on exam. JAK2 mutation is negative, and a bone marrow biopsy confirms myelofibrosis

Which statement is true regarding treatment options:

A. Given the negative JAK2 status Ruxolitinib should be avoided

B. JAK2 negative MF carries a poor prognosis, and should be treated with stem cell transplant

C. Hydroxyurea is the only effective treatment for JAK2-negative myelofibrosis

D. Ruxolitinib efficacy is not dependent on JAK2 status

Only 50% of MF is JAK2 positive but Ruxolitinib is effective regardless of JAK2 mutation status

Question 9: MPN Management

A 67 year old with Essential Thrombocytosis has had platelet counts near 700,000/uL for over 20 years. He is on 81mg ASA with no thrombotic complications. A recent CBC shows platelets at 74,000/uL. A repeat 2 weeks later is 63,000/uL. He also notes some early satiety and left sided abdominal pain.

What is the next step in management?

A. CT Abdomen/Pelvis

B. GI referral for endoscopy

C. Bone Marrow Biopsy

D. Increase aspirin dose to 325mg

Roughly 15% of patients with Essential Thrombocythemia or Polycythemia vera can transform into Post-ET or Post-PV Myelofibrosis

Post-PV and Post-ET Myelofibrosis

15% of PV and ET over a 10 year span will transform into Myelofibrosis

Requires immediate restaging for risk of AML transformation and if appropriate referral for stem cell transplant

Even if symptoms are minimal, Ruxolitinib has been shown to improve post-SCT outcomes, so patients are usually started on it as a bridge while a donor is identified

In our practice we continue Ruxolitinib through transplant and for up to 2 years after transplant

Summary

CML

- MPN defined by t(9;22) Philadelphia chromosome
- Treatment has been revolutionized with TKI therapy
- Future directions include optimizing ways to shorten duration of therapy

PV and ET

- MPNs with long life expectancy
- Treatment emphasis on controlling vasomotor symptoms and thrombotic risk
- Aspirin, Hydroxyurea, Phlebotomy (PV) ,and Ruxolitinib (PV) mainstays of therapy
- Always be wary of PV/ET with new cytopenias as could be transformation to MF

MF

- MPN with short life expectancy due to high risk of AML transformation
- Risk stratification based on molecular mutations
- Ruxolitinb is the primary treatment with allogeneic stem cell transplant as only cure

Disease	Mutation	Lab Presentation	Clinical Presentation	Treatment
Chronic Myeloid Leukemia	t(9;22) Philadelphia Chromosome	High WBC, eosinophils, basophils, +/- blasts	Splenomegaly	• TKIs • Stem cell transplant
Polycythemia Vera	JAK2 (95%)	Increased Hgb	Itching, flushing, splenomegaly	• Phlebotomy • Hydroxyurea • Ruxolitinib
Essential Thrombocytosis	JAK2 (50%)	Increased platelets	Vasomotor symptoms, Thrombosis, bleeding risk if platelets > 1M	• Aspirin • Hydroxyurea
Myelofibrosis	JAK2 (50%) CALR (25%) MPL (5%)	pancytopenia	Splenomegaly, bone marrow fibrosis	• Ruxolitinib • Fedratinib • Stem cell transplant

Thank You !

Jonathan.abbas@bannerhealth.com

(706) 495-6178