Myeloid Neoplasms and Leukemia

SESSION OBJECTIVES:

Use these session objectives to test your knowledge of the important concepts presented in this chapter and as study topics to return to prior to your exams.

1. Describe available tools applied in the diagnosis and classification of hematopoietic neoplasms (please review: Diagnosing Hematolymphoid Neoplasms.
2. Distinguish a mature from immature (i.e., blast) hematopoietic cell in the peripheral blood by morphology.
3. Describe the major categories of myeloid stem cell neoplasms and understand the clinical presentation and diagnosis of select examples of these disorders.
4. Explain the mechanism of action and clinical uses for tyrosine kinase inhibitors and All-trans retinoic acid (ATRA).
5. Describe the abnormal morphology and clinical features associated with myelodysplastic syndromes.

OPTIONAL PRE-CLASS MATERIALS FOR THIS SESSION:

- Chapter 19: Introduction to Hematologic Malignancies
- Chapter 20: Myeloproliferative Neoplasm and Myelodysplastic Syndromes
- Chapter 21: Acute Leukemias

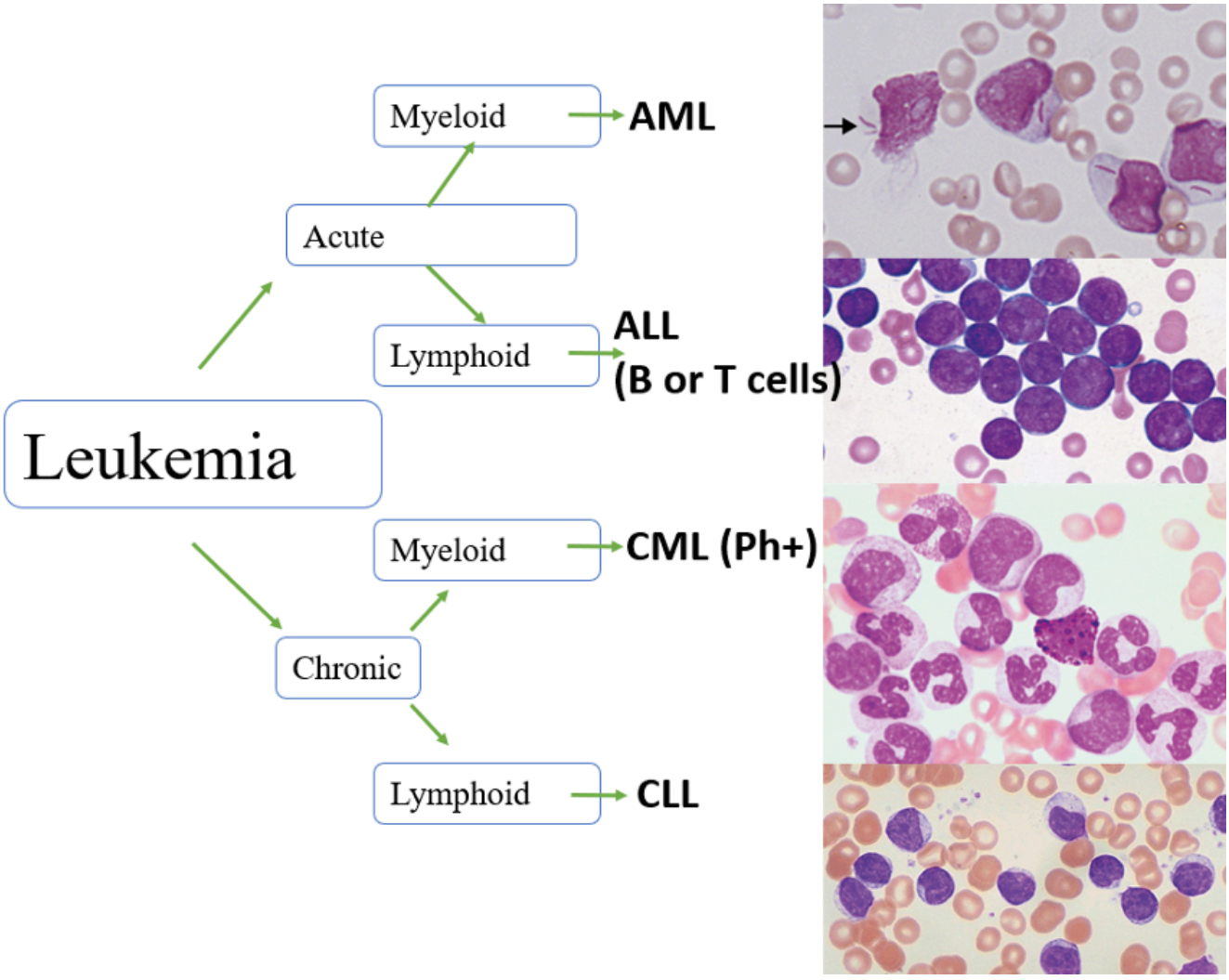
A brief forward: Many thanks to Dr. Corliss Newman, MD for contributing this material.

OVERVIEW

Myeloid neoplasms are hematologic malignancies originating from myeloid precursor cells, which give rise to granulocytes, erythrocytes, monocytes, and megakaryocytes. These diseases range from indolent disorders to aggressive malignancies, and are generally classified into three main categories: **Myelodysplastic Syndromes (MDS)**, **Myeloproliferative Neoplasms (MPNs)**, and **Acute Myeloid Leukemia (AML)**. Diagnosis relies on clinical evaluation, morphology (peripheral blood and bone marrow), immunophenotyping, and genetic testing.

Leukemia refers to disorders characterized by the uncontrolled production of clonal white blood cells, with malignant cells losing their ability to differentiate and instead self-renew. This leads to the suppression of normal stem cell function in the bone marrow.

- **Acute Leukemias** are aggressive and tend to arise from malignant transformation of early stem cells/ progenitor cells. Examples include **Acute Myeloid Leukemia (AML)** and **Acute Lymphoid Leukemia (ALL)**, both of which have multiple subtypes. Patients with acute leukemias require treatment immediately, as these patients will otherwise likely die from their disease in a matter of days to weeks.
- **Chronic leukemias**, which include **Chronic Myeloid Leukemia (CML)** and **Chronic Lymphocytic Leukemia (CLL)**, tend to arise from malignant transformation of later progenitor cells or mature cells and are typically slower-growing and indolent.
    - In **CLL**, the previously reviewed disorder of mature lymphocytes, therapy is often deferred until patients are symptomatic- allowing some patients to live for years without treatment.
    - **CML** requires treatment soon after diagnosis to prevent progression to a blast crisis, though treatment is not an emergency. If not treated, most patients with CML will progress to a blast crisis phase and a more aggressive disease similar to AML over the course of a few years. Treatments with targeted therapy in CML have dramatically changes outcomes for these patients, such that they can avoid transformation to blast crisis and lead long, perhaps even normal, lives—more to come below!



CLONAL HEMATOPOIESIS

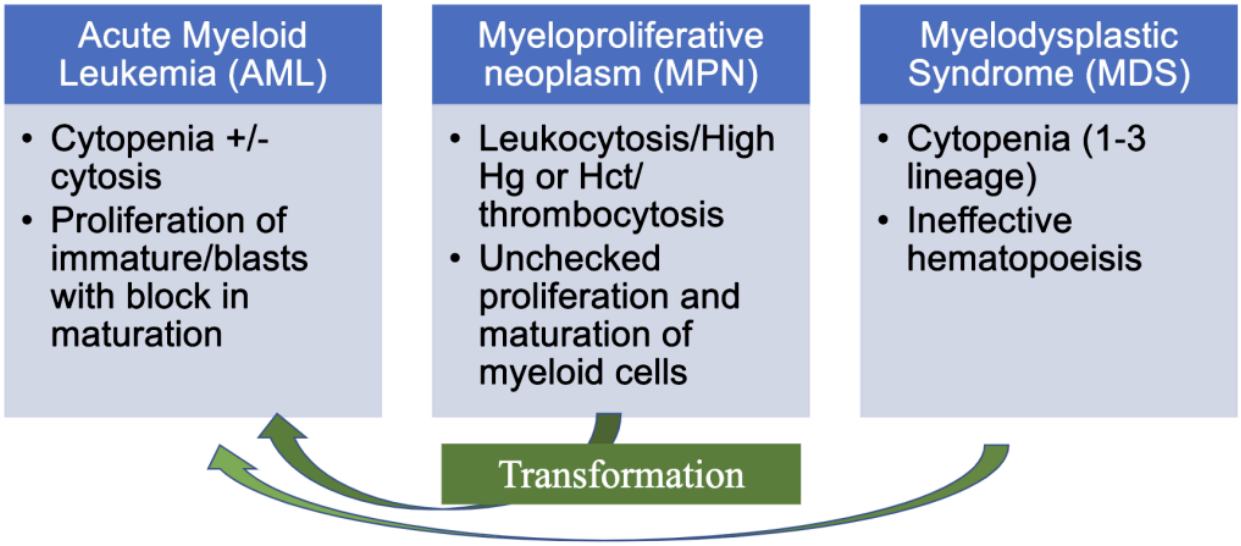
Clonal Hematopoiesis refers to the production of blood cells from a single stem or precursor cell, in contrast

to normal hematopoiesis, which arises from multiple stem cells. As we age, some stem cells may die or acquire mutations that give them a survival advantage, leading to clonal expansion (i.e. clonal hematopoiesis). While clonality is a hallmark of malignancy, it doesn't always indicate cancer. For example, **Paroxysmal Nocturnal Hemoglobinuria (PNH)** is a disorder of clonal hematopoiesis caused by a mutation in the **PIGA** gene, leading to deficient **GPI-anchored** proteins like CD55 and CD59. This results in complement-mediated hemolysis but does not classify as malignancy, as cell differentiation and function remain largely preserved.

Clonal Hematopoiesis of Indeterminate Potential (CHIP) is defined as the presence of clonally expanded hematopoietic stem cells with leukemogenic mutations in individuals without signs of hematologic malignancy, dysplasia, or cytopenia. It carries a 0.5-1.0% risk per year of progressing to leukemia. Approximately 80% of CHIP cases involve mutations in genes such as ***DNMT3A***, ***TET2***, ***ASXL1***, DNA damage repair genes like ***PPM1D*** and ***TP53***, the regulatory tyrosine kinase ***JAK2***, or mRNA spliceosome components ***SF3B1*** and ***SRSF2***. CHIP is linked to a pro-inflammatory state associated with coronary artery disease, myocardial infarction, venous thromboembolism, and poorer outcomes in conditions like aortic stenosis and heart failure. Risk factors include age, genetic predisposition, smoking, obesity, inflammatory conditions, premature menopause, HIV and exposure to cancer therapies. Interestingly, clonal hematopoiesis with additional non-PIGA somatic gene alterations occurs in patients with Aplastic Anemia and PNH clones, as well as patients with PNH who progress to other bone marrow problems.

Continuum of changes in bone marrow that define myeloid neoplasms: Myeloid neoplasms develop as bone marrow cells accumulate mutations over time that affect their clonality, differentiation, and proliferative capacity.

- **Acute Myeloid Leukemia (AML)** shows significant blast proliferation (≥20% blasts in bone marrow or peripheral blood) and loss of differentiation capacity, leading to severe anemia, thrombocytopenia, and leukopenia.
- **Myeloproliferative Neoplasms (MPNs)** are characterized by the overproduction of mature, differentiated cells; examples include excess red blood cells (Polycythemia Vera), platelets (Essential Thrombocythemia), white blood cells (Chronic Myelogenous Leukemia and Chronic Myelomonocytic Leukemia), and fibrous material in the bone marrow stroma (Myelofibrosis). While the initial issue is clonal overproduction, these disorders can progress to bone marrow failure or acute leukemia.
- **Myelodysplastic Syndromes (MDS)** involve impaired production of mature cells in the bone marrow due to clonal mutations. Patients may present with varying degrees of anemia, thrombocytopenia, or leukopenia. By definition, the blast count remains below 10%, but over time MDS can progress to acute leukemia.



Workup of Myeloid Neoplasms:

The detailed workup of hematologic malignancies, including diagnostic tools and testing strategies, has been thoroughly covered in the detail in Diagnosing Hematolymphoid Neoplasms. In brief:

1. **Clinical History:** The patient's background and symptoms.
2. **Histology:** Examination of bone marrow aspirate/biopsy preferred, but peripheral blood can be used if a biopsy cannot be obtained.
    - In diagnosing AML, the presence of **Auer rods** (needle-like cytoplasmic inclusions from the abnormal fusion of azurophilic granules) is a key morphological feature that indicates the blasts are of **myeloid origin**. In **APL**, promyelocytes often have distinctive morphology with numerous coarse azurophilic granules and Auer rods, helping to distinguish this subtype
3. **Immunophenotyping:** Identifies cell types and can be done on bone marrow or peripheral blood using immunohistochemistry and flow cytometry.
    - **Markers of cell immaturity** (early precursor cells): **CD34, TdT**
    - **Markers of myeloid origin**: **CD117, CD13, CD15, CD33, MPO** (myeloperoxidase), **CD14, CD64, Glycophorin A, CD41, CD61**
    - **Markers of Lymphoid origin**:
        - **B-cell markers**: **CD19, CD20**; if the B-cell population is clonal, then all the cells will express either **Kappa** or **Lambda** light chains.
        - **T-cell markers**: **CD2, CD3, CD4, CD5, CD7, CD8**
4. **Genetics**: VERY important in the diagnosis of AML, as they define prognosis and impact treatment decisions.
    - **Karyotyping** is a method to examine chromosomes during cell division. Cultured dividing cells are analyzed in metaphase to detect numerical and structural abnormalities. About 20 metaphases are typically reviewed. Although less sensitive than other genetic tests, karyotyping is useful for identifying large chromosomal changes.
    - **Fluorescent in situ hybridization (FISH)** detects specific chromosomal rearrangements that may not be visible by karyotyping. It uses fluorescent probes to identify known gene mutations and provides

faster results than karyotyping. However, FISH requires prior knowledge of the genes being targeted.
    - **Molecular Methods** (example: Gene sequencing): PCR can look for smaller gene mutations and can be done relatively quickly.

ACUTE LEUKEMIA

The diagnosis requires ≥20% blasts in bone marrow or peripheral blood, though some genetic findings allow for lower blast percentages.

Acute Myeloid Leukemia

AML is an aggressive cancer characterized by the overproduction of early myeloid precursor cells (e.g., myeloblasts, promyelocytes, monoblasts, megakaryocytes) in the bone marrow, and indeed the subtype of AML was based upon the type of blast that was predominant in the bone marrow (the old FAB system, as discussed below). AML causes anemia, neutropenia, and thrombocytopenia by replacing normal bone marrow with non-maturing blasts, leading to impaired blood cell production and creating a medical emergency due to infection risks, severe anemia, and bleeding.

Clinical symptoms and signs of AML:

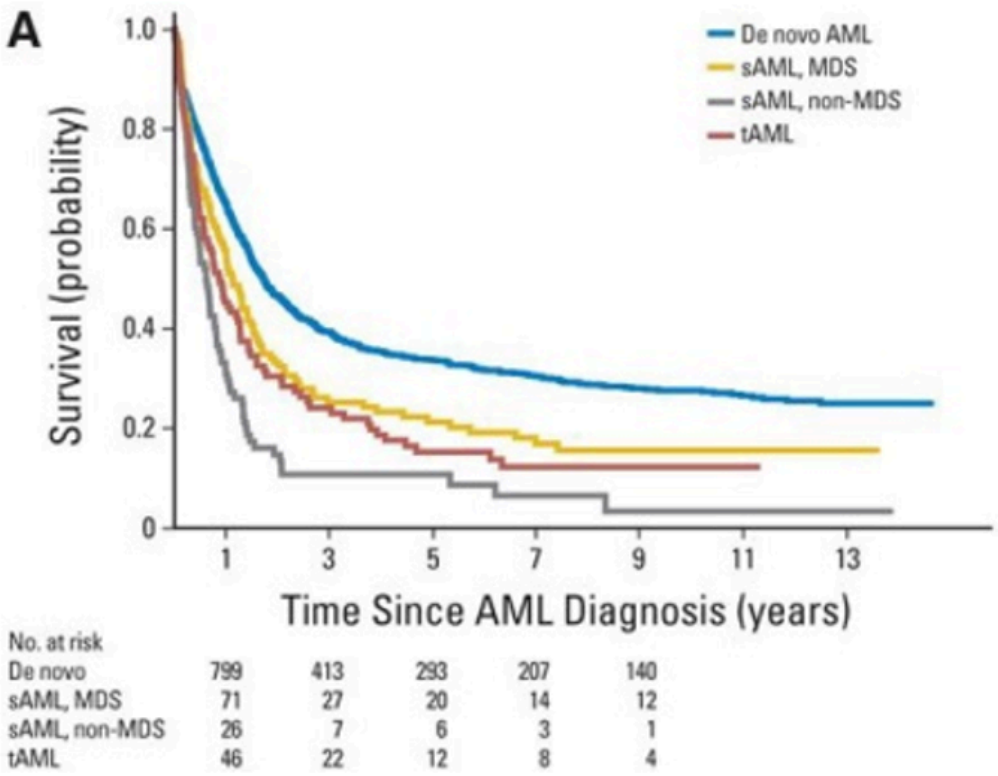
- **WBCs:** WBCs can be elevated, decreased or normal; blasts >/= 20% is diagnostic for AML.
- **Neutropenia** (actual or functional): This is often associated with fever, chills, localized infectious symptoms.
- **Anemia**: This is often associated with patient symptoms including pallor, weakness, fatigue, dyspnea on exertion.
- **Thrombocytopenia**: Lack of platelets or low platelets can lead to bleeding, bruising, petechiae.
- **Expansion of bone marrow medullary cavity:** This can cause bone pain.
- **Constitutional symptoms:** Patients may present with night sweats, weight loss, poor appetite.
- **Extra-medullary disease:** Leukemia cells can infiltrate areas outside the bone marrow including infiltration of skin (leukemia cutis), soft tissue (a.k.a. myeloid sarcoma, chloroma, granulocytic sarcoma), gums, and the CNS and other organs.
- **Coagulopathy:** It is very important to consider (and often presumptively treat) Acute Promyelocytic Leukemia in a patient who presents with coagulopathy (as we'll discuss later).

Epidemiology: AML predominantly affects older adults (median age: 69). It often follows myelodysplastic syndrome or a myeloproliferative disorder. Younger patients (20s-30s) are more likely to present with de novo AML, which has a better prognosis compared to secondary forms.

Risk Factors for AML:

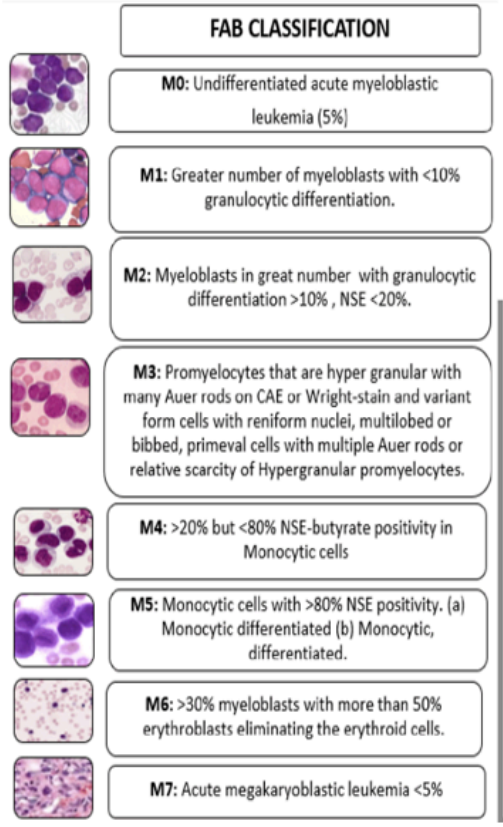
- Prior chemotherapy/radiation (therapy-related AML or tAML)
- Antecedent hematologic disorders (secondary AML or sAML)
- Genetic predisposition (Down syndrome, Blooms syndrome, Fanconi anemia, Neurofibromatosis, Noonan syndrome)
- Smoking
- Chemical exposure (e.g., benzene)

NOTE: AML with prior exposures (e.g., chemotherapy, radiation) or prior hematologic conditions typically has a worse prognosis than de novo AML (as demonstrated by Kaplan-Meir plot below).



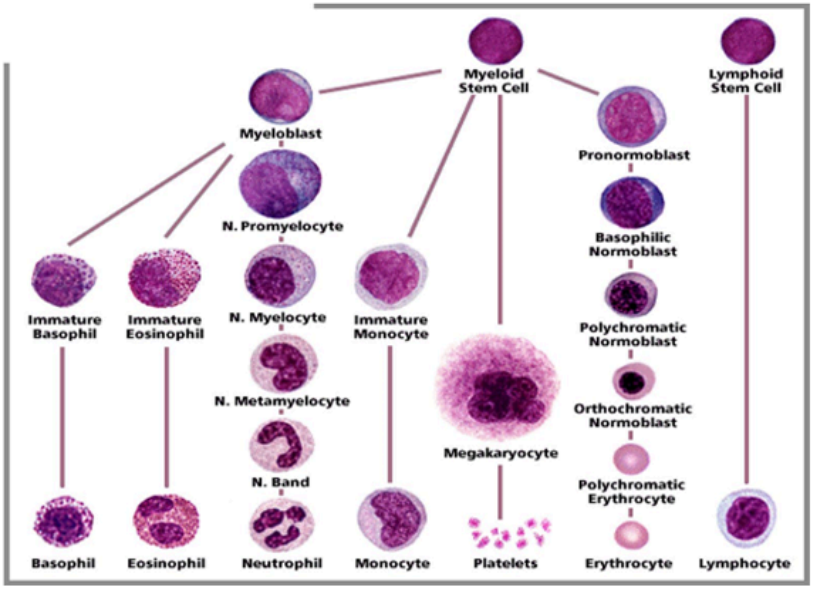
Classification schemes for AML

Legacy classification: In the past, AML was classified by the morphology of leukemic cells using the FAB (French/American/British) system. The FAB M3 classification (now known as Acute Promyelocytic Leukemia, or APL) was associated with a higher risk of Disseminated Intravascular Coagulation (DIC). While the FAB system is no longer used for treatment or prognosis (except for APL), it is still prominent in older literature.



Legacy morphologic classifications (French/American/British) are poorly correlated with outcomes, with the exception of FAB M3 – APL.

Cytogenetics are more predictive of disease risk.



Current AML Classification (2022 ELN): AML is now classified by **blast count and genetic abnormalities**, with genetic findings strongly influencing treatment options and prognosis. Patients with favorable genetics may be treated successfully with chemotherapy and immunotherapy, while those with unfavorable genetics may require stem cell transplants or experimental therapies for a chance of cure. Patients with the t(15;17) translocation, defining Acute Promyelocytic Leukemia, have an excellent prognosis with treatment and are likely to be cured without the need for an upfront bone marrow transplant.

Other AML types are classified as favorable, intermediate, or unfavorable based on their genetics. Patients with favorable genetics are treated with chemotherapy and immunotherapy, often avoiding transplant upfront. Those with unfavorable genetics typically require stem cell transplants or experimental therapies for a chance at a cure.

Table 6. 2022 European LeukemiaNet (ELN) risk classification by genetics at initial diagnosis[a]

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*[b,c] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*[b,c] • Mutated *NPM1*[b,d] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*[e]
Intermediate	• Mutated *NPM1*[b,d] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[b,f] • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged[g] • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype,[h] monosomal karyotype[i] • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*[j] • Mutated *TP53*[k]

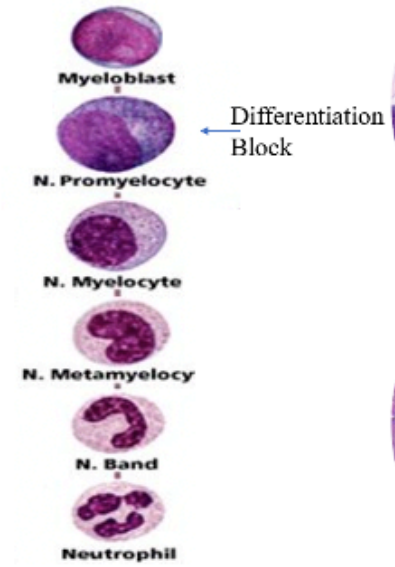
Treatment of AML (excluding APL):

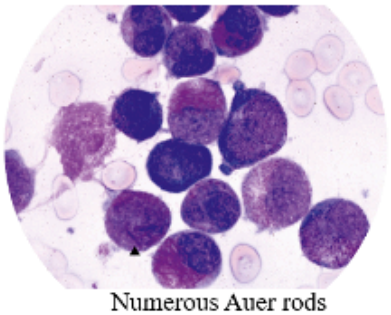
AML that lacks the APL-defining **t(15;17) translocation** is typically treated with chemotherapy in medically fit patients. The standard **induction therapy** includes the "7+3" regimen—7 days of continuous cytarabine infusion combined with 3 days of daily anthracycline (often daunorubicin). For **CD33-positive** AML with favorable or intermediate genetics, **Gemtuzumab ozogamicin** (an anti-CD33 antibody) is added. For **FLT3-mutated** AML, a targeted **FLT3 inhibitor** (e.g., midostaurin or quizartinib) is included. After induction, further consolidation or stem cell transplant is based on response to therapy and genetic risk factors.

Acute Promyelocytic Leukemia (APL):

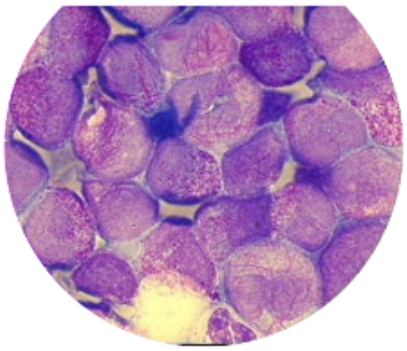
APL is caused by a fusion between PML (a protein normally involved in regulation of gene activity) and RARA (a retinoic acid receptor). ***PML*::RARA fusion** from a translocation between chromosomes 15 and 17. This mutation blocks promyelocyte differentiation, leading to a buildup of immature, malignant cells that can cause **disseminated intravascular coagulation (DIC)**. The hallmark finding is numerous promyelocytes with **Auer rods** in the bone marrow. APL is dangerous due to rapid development of DIC, often fatal without early intervention. **All-trans retinoic acid (ATRA)** should be started immediately upon suspicion of APL, even before diagnosis is confirmed. ATRA overcomes the differentiation block, allowing promyelocytes to mature into neutrophils and preventing DIC.

APL: Acute promyelocytic leukemia: t(15;17) with *PML/RARA* fusion gene.





Numerous Auer rods



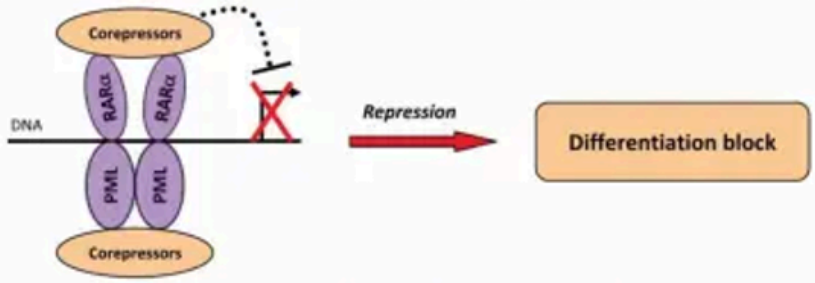
- Mutation causes block of onward maturation from promyelocyte to segmented neutrophil.
- 10-15% of all adult AML; median age 40 years.
- Associated with DIC; delayed diagnosis and treatment can lead to death.

ATRA Treatment:

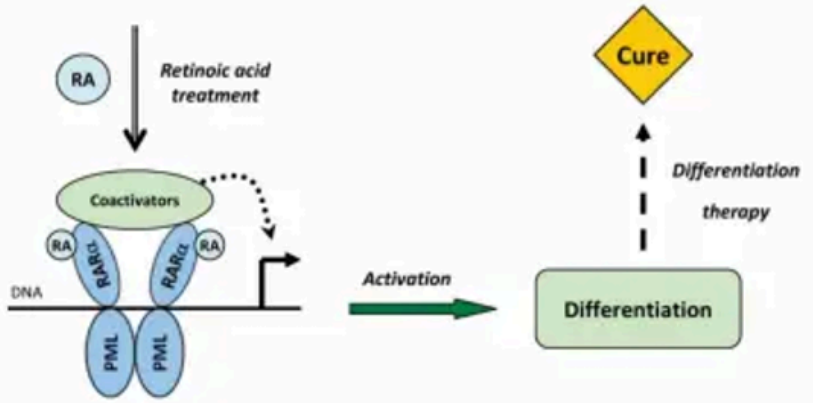
ATRA binds to the retinoic acid component of the **PML::RARA fusion protein**, lifting the differentiation block and allowing promyelocytes to mature into neutrophils. This treatment has three effects:

1. **Curing the leukemia** by converting malignant promyelocytes into neutrophils.
2. **Stopping DIC** by eliminating promyelocytes.
3. Triggering a **cytokine storm** (differentiation syndrome), which can resemble septic shock and rarely causes multi-organ failure.

Though ATRA induces remission, it is not fully curative on its own. Historically, APL was treated with chemotherapy plus ATRA, but now the combination of **ATRA and arsenic** is preferred for better outcomes. (I*magine how the conversation might go with a new patient shortly after you introduce yourself to them as their doctor, the discussion regarding their diagnosis of AML and the need for immediate treatment. Now imagine telling them that you are going to be starting them on Arsenic, a known poison used to kill people in novels/real life crimes, plus another drug called ATRA, which is basically a form of vitamin A that can also be toxic. This is definitely a trust-building exercise between you and your patient as they start on this journey!*)



#1) Acute Promyelocytic Leukemia: The **PML-RARA fusion protein** silences genes in promyelocytes, which prevents their differentiation. This causes promyelocytes to become immortal and replicate indefinitely, leading to leukemia.



#2) Treatment with **Retinoic Acid (RA)** causes a shift in the PML-RARA fusion protein, which eventually causes *differentiation* of promyelocytes into neutrophils. This breaks the ongoing replication of promyelocytes, thereby curing the leukemia. (Ablan J, Blood 2011; 117:5795)

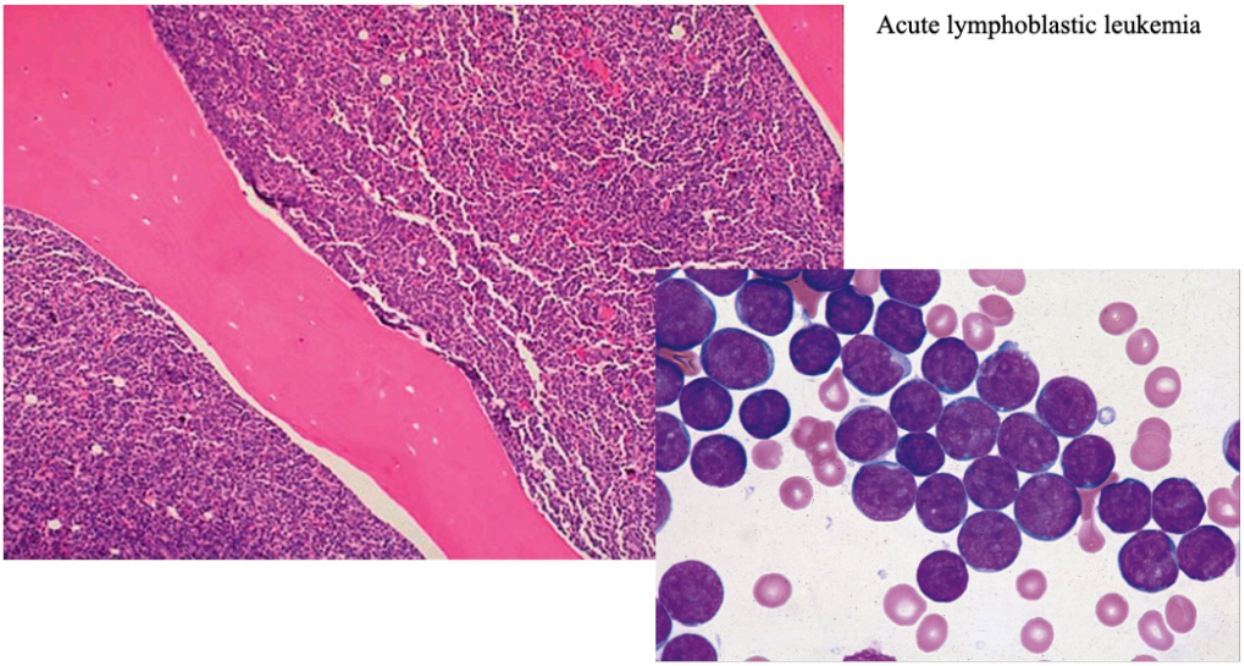
(AN ASIDE: Acute Lymphoblastic Leukemia)

Lymphoid neoplasms are not included in the classification of **myeloid neoplasms**. When referring to **myeloproliferative disorders**, we are specifically talking about the proliferation of cells from the **myeloid cell line**, in contrast to neoplasms arising from **lymphoid cell precursors**. However, **ALL** is discussed here as a contrast to **AML**, given their similar presentation as acute leukemias but with different cell line origins. **Chronic Lymphocytic Leukemia (CLL)**, which also arises from lymphoid cells, was addressed in the **lymphoma materials**.

- **Clinical Presentation:** ALL is more commonly seen in children than in adults (**B-cell ALL** peaks ~3 years of age, while **T-cell ALL** peaks in adolescence). It may present as a leukemic form, a lymphoma form, or both. Patients often have symptoms related to **cytopenias** (neutropenia, anemia, thrombocytopenia) which can lead to infections, fatigue, and bleeding. **Adenopathy** and **mediastinal masses** can cause complications like airway or superior vena cava compression.
- **Histology:** Immature lymphoblasts typically have a **high nuclear-to-cytoplasmic ratio**, with a large nucleus and a thin rim of agranular cytoplasm. Nucleoli may be present. The bone marrow is often packed with these immature cells.
- **Immunophenotype:** ALL/LBL is divided into **B-cell** or **T-cell** subtypes, and immunophenotyping is required to distinguish them, as the morphology is indistinguishable. **NK-cell lineage** is rarely seen.
- **Genetics:** The presence of the **t(9:22) translocation (BCR::ABL)** is a key finding in some cases of ALL. This mutation, also associated with CML, can occur in ALL patients, especially in adults, and requires targeted

therapy in addition to chemotherapy. Adult patients with Philadelphia chromosome-positive ALL may have progressed from prior CML into blast crisis.

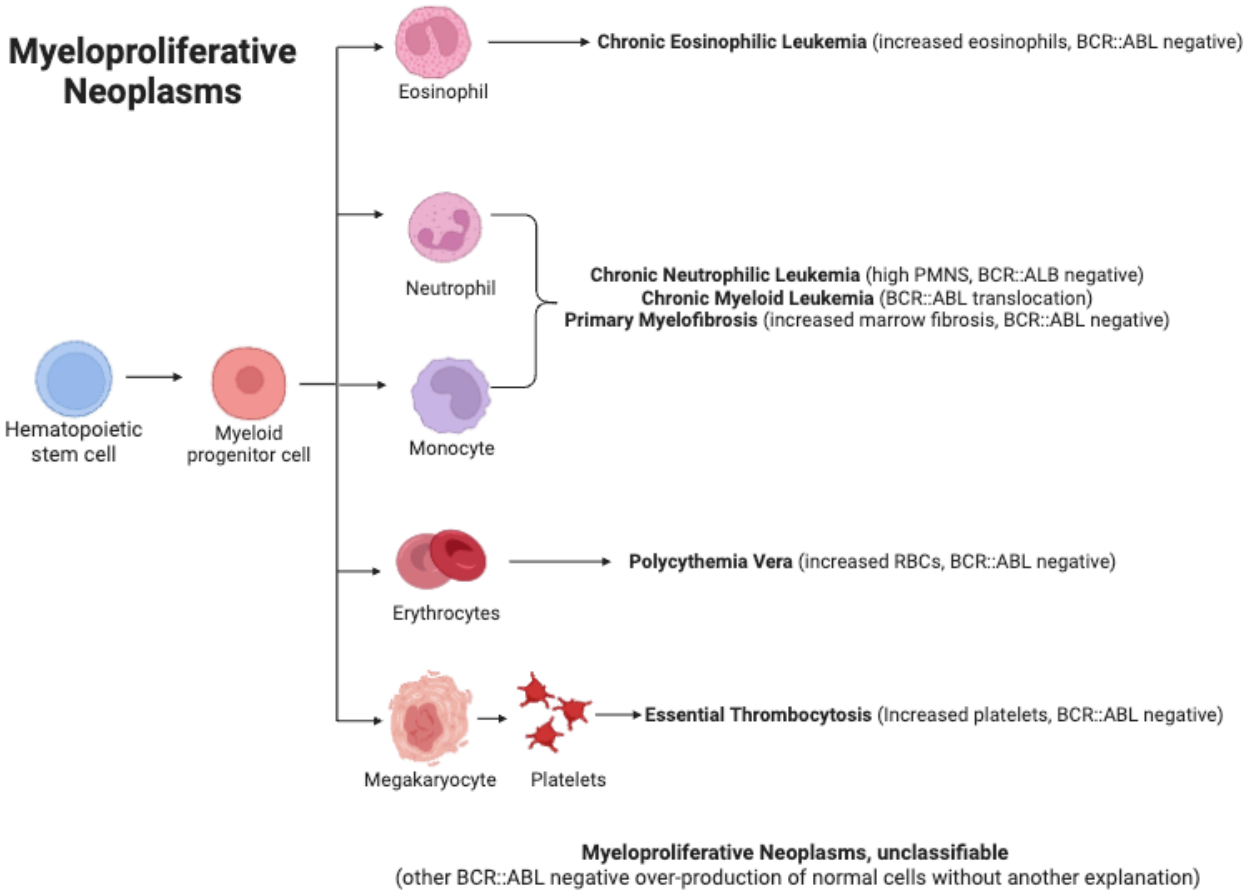
- **Treatment:** Treatment generally involves **chemotherapy**. In cases where the **BCR::ABL** translocation is present, therapies like **imatinib** or other **BCR::ABL inhibitors** are used in combination with chemotherapy.
- **Prognosis**: while the leukemic/lymphomatous cells are aggressive, it has a better prognosis in children (than in adults).



Acute lymphoblastic leukemia

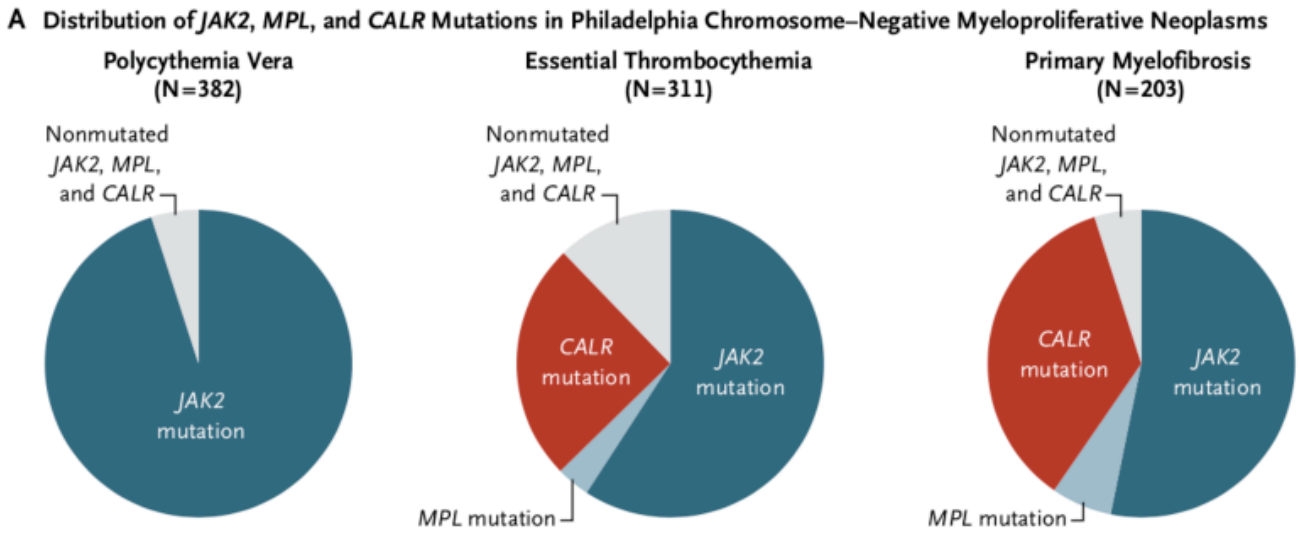
MYELOPROLIFERATIVE NEOPLASMS

Myeloproliferative Neoplasms (MPNs) are disorders where the bone marrow overproduces normal-appearing, mature blood cells such as red blood cells, platelets, and white blood cells (excluding lymphocytes and plasma cells). In **myelofibrosis**, cell counts may be high or low. Diagnosis is based on clinical evaluation, lab tests, and bone marrow analysis. As per the 2016 WHO classification, these are the following Myeloproliferative Neoplasms:



In MPNs, growth-factor independent proliferation occurs, but differentiation remains intact, leading to increased production of mature blood cells. The bone marrow is typically **hypercellular**, except in myelofibrosis (where fibrosis can crowd out healthy cells). **Extramedullary hematopoiesis** (usually in the spleen or liver) may result in **organomegaly**. MPNs carry a variable risk of transforming into acute leukemia or entering a **"spent phase"**, where the bone marrow becomes **hypocellular** with increased **fibrosis** and stops producing adequate blood cells.

CML is defined by the **BCR::ABL translocation**, while PV, ET, and PMF are often associated with **JAK2**, **CALR**, or **MPL mutations**. Overlap in cell overproduction can occur, such as elevated neutrophils, basophils, eosinophils, platelets, and red cells in CML. The presence of the **BCR::ABL translocation** is required to diagnose CML. ***NOTE: CML will be covered in your lecture, while PV and ET may be further covered in small groups.***

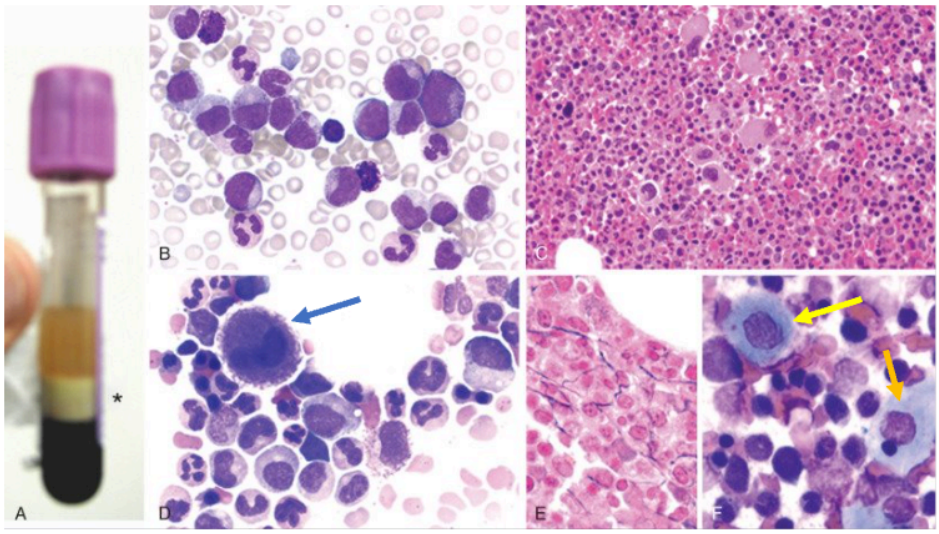


***JAK2* mutations**: Mutations of the tyrosine Janus Kinase 2 (*JAK2*), a gene found on the short arm of chromosome 9), can cause hematopoietic progenitor cells in myeloproliferative neoplasms to be hypersensitive to growth factors and other cytokines. The most common *JAK2* mutation, V617F, causes cytokine-independent activation of JAK-STAT, activation of other pathways implicated in erythropoietin receptor signaling, and affects the PI3-Kinase pathway that regulates apoptosis.

***CALR* mutations**: Calreticulin is a calcium-binding protein localized in the endoplasmic reticulum (ER) primarily, but also is found in the nucleus, cell membranes, and extracellular matrix. *CALR* mutations have been found in about 70% of patients with ET or PMF who don't have JAK2 or MPL mutations. Normal functions of calreticulin include proper folding of newly synthesized glycoproteins within the ER and modulating calcium homeostasis. Mutations in *CALR* associated with ET and PMF disrupt the calcium-binding and endoplasmic reticulum retention domains. These mutations appear to alter the protein's function, resulting in cytokine-independent growth and activation of the JAK-STAT signaling pathway. Mutant *CALR* also interacts directly with the thrombopoietin receptor (MPL), resulting in constitutive activation of MPL and downstream signaling molecules in the JAK-STAT pathway.

MPL mutations: Activating mutations in MPL, which encodes the thrombopoietin receptor (TPO-R) have been found in patients with familial ET and have also been found in patients with non-familial ET and PMF.

- Chronic myeloid leukemia
  - **Clinical Presentation:** The peak incidence of CML occurs in the 5th to 6th decade of life, but is also rarely seen in adolescents. Patients present with elevated WBCs, especially neutrophils, eosinophils, and basophils. Splenomegaly and constitutional symptoms like fatigue, weakness, or weight loss may occur. Occasionally, patients will present with elevated platelets or RBCs without high WBCs, but that is quite rare.
  - **Histology:** Peripheral blood usually shows elevated WBCs with increased neutrophils, basophilia (increased basophils), anemia, and possibly elevated or decreased RBCs or platelets.



A: Increase buffy coat

B: High WBC

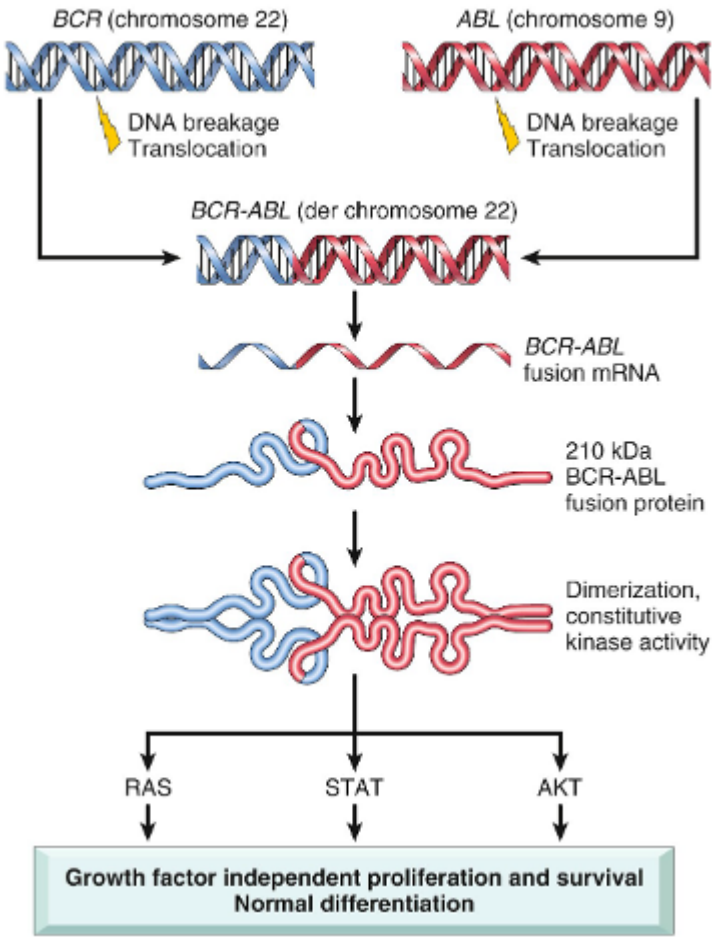
C: Hypercellular BM with granulocytic hyperplasia and small Megs.

D: Aspirate smear of BM with micromegs (arrow).

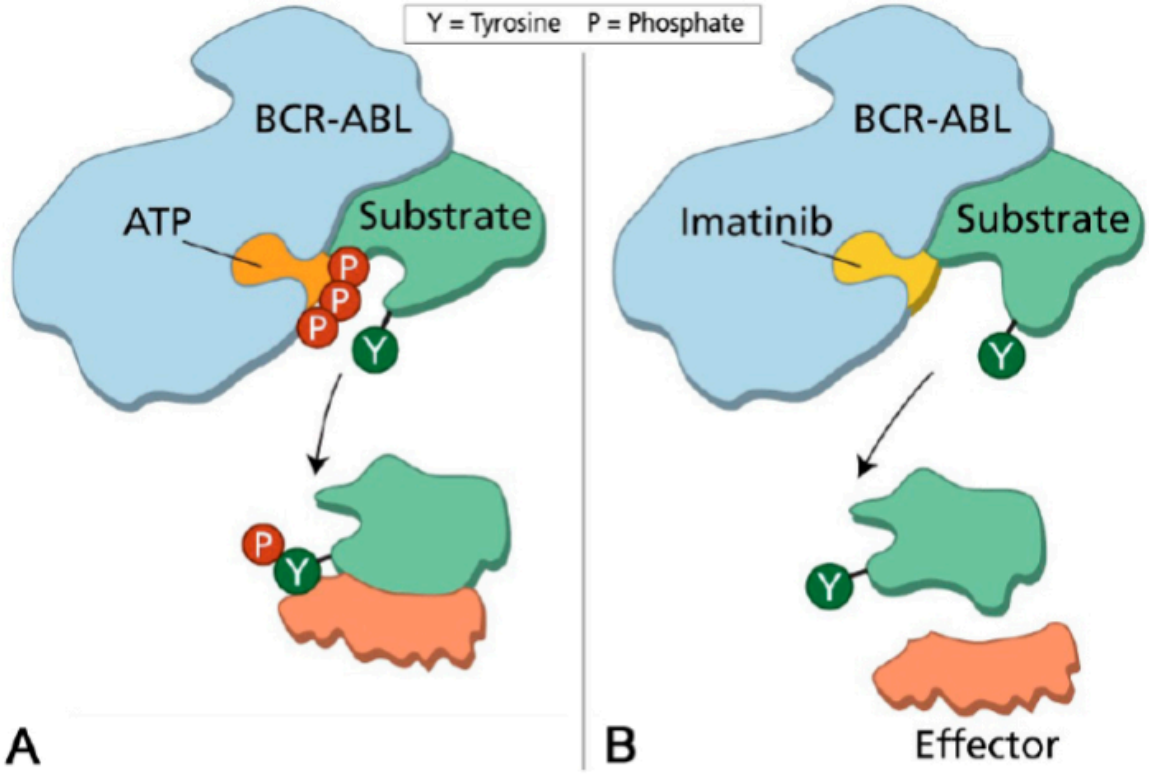
E: Mild BM fibrosis (black in color).

F: Pseudo-Gaucher cells (arrows).

- **Genetics:** CML is defined by the presence of the ***BCR*::*ABL* fusion gene**, resulting from a translocation between chromosomes 9 and 22 (Philadelphia chromosome). The fusion gene produces an unregulated tyrosine kinase (*BCR*::*ABL*) protein that is involved in many signal transduction pathways such as growth, apoptosis, and adhesion defects. The *BCR*::*ABL* fusion gene has three main forms (P190, P210, P230), each caused by a different breakpoint, with P210 being most common (followed by P190).

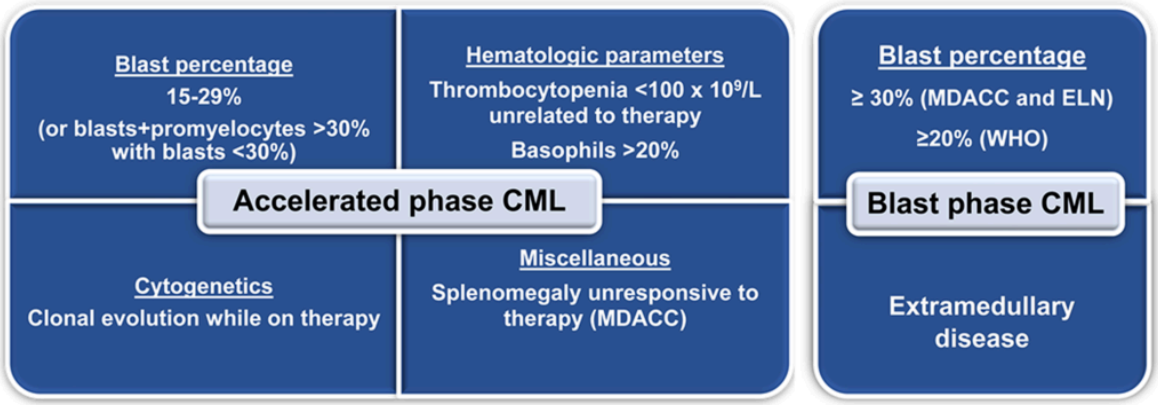


- **Treatment:** Historically, CML was treated with interferon, hydroxyurea (to lower counts), or allogeneic stem cell transplant (20% mortality risk). However, **tyrosine kinase inhibitors (TKIs)** like **Imatinib** (brand name Gleevec, experimental name was STI571) and second-generation drugs (e.g., dasatinib, nilotinib, bosutinib), which are BCR::ABL inhibitors, have revolutionized treatment, providing near-normal life expectancy.



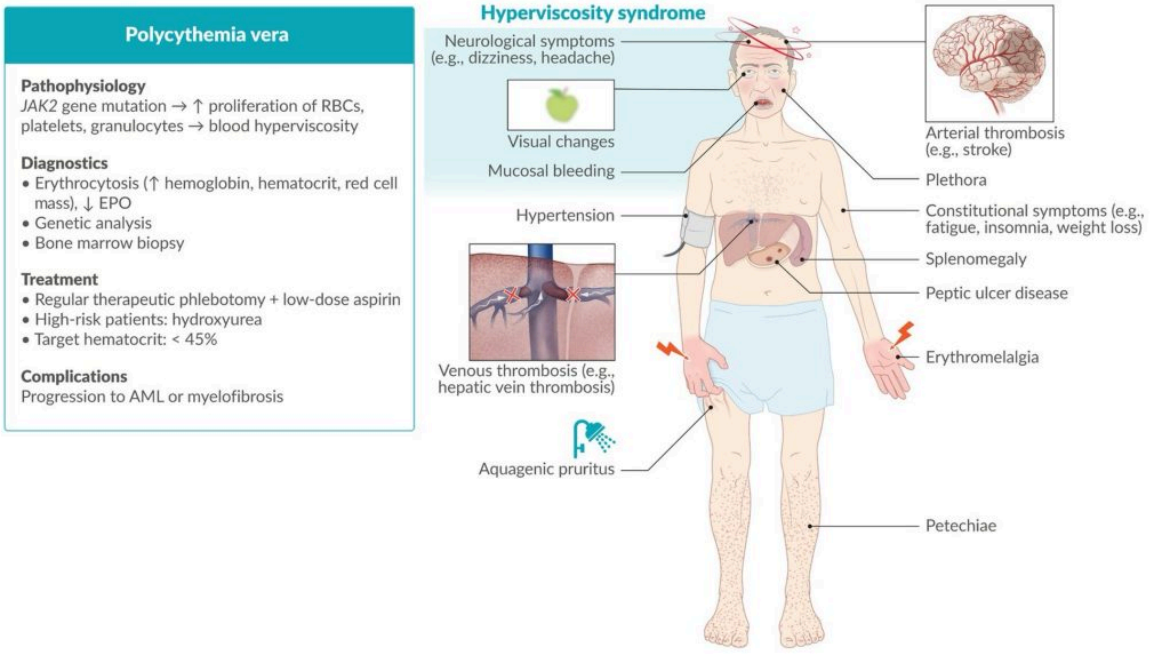
Mode of action of imatinib. The phosphorylation of a substrate is shown schematically. ATP occupies the pocket in the ABL component of BCR-ABL oncoprotein. The substrate then detaches itself from the BCR-ABL oncoprotein and makes functional contact with a further downstream effector molecule. When imatinib occupies the ATP binding site, it prevents phosphorylation of the substrate. This molecule in turn fails to make contact with the effector protein and the signal transduction pathway that would otherwise transmit the 'leukemia signal' is interrupted [published, with permission from Goldman & Mughal, Chronic Myeloid Leukaemia, Ed: Hoffbrand, Tuttenham & Catovsky, Blackwell Science, Oxford, UK (2005)].

- **Prognosis:** Without treatment, ~ 50 % of CML progresses to **blast crisis** (10-19% bone marrow blasts and worsening blood counts; median survival = 3 years) while the remaining 50% enter **accelerated phase** (which will eventually progress to blast phase). These blast phase leukemias (70% are AML and 30% are ALL) are aggressive and hard to cure. Hence, treatment is very important.



Note that the classification of accelerated phase CML by blast percentages varies with some different classification schemes. The WHO (World Health Organization) classification, uses 20% blasts as the definition for blast phase CML.

- **Polycythemia Vera (P. Vera, PV)**
  - **Clinical Presentation:** P. Vera typically presents with elevated RBC, hemoglobin (hgb), and hematocrit (HCT). Most patients are diagnosed incidentally through routine CBC, but symptoms can include headaches or vision changes (due to increased blood viscosity), splenomegaly (resulting in early satiety), itching, or bleeding/thrombosis. The median age of diagnosis is around 60.
  - **Histology:** Bone marrow shows hypercellularity with increased red blood cell production.
  - **Laboratory studies:** Elevated RBCs and low erythropoietin (EPO) levels are characteristic, as the kidneys suppress EPO in response to excess RBC production.
  - **Genetics:** P. Vera is commonly associated with **JAK2 V617F mutations**, which drive overproduction of red blood cells independent of normal growth signals.
  - **Treatment:** First-line treatment includes **phlebotomy** to lower Hgb/HCT. **Hydroxyurea** therapy can be instituted to suppress over production of RBCs and is the mainstay of therapy for patients with P. Vera once the high blood count has initially been brought down with phlebotomy.
  - **Differential Diagnosis:** Conditions causing **secondary polycythemia** include **hypoxia** (e.g., high altitude, lung disease, sleep apnea), right-to-left heart shunts, and EPO-secreting tumors (e.g., renal cell carcinoma, hepatocellular carcinoma, and cerebellar hemangioblastomas). These conditions will show **normal or elevated EPO** levels, in contrast to P. Vera's low EPO. **Dehydration** can also cause falsely elevated RBC levels due to reduced plasma volume.



- **Essential Thrombocythemia (ET):**
  - **Clinical Presentation:** ET is a **BCR::ABL-negative** myeloproliferative neoplasm characterized by excessive clonal platelet production. It is often diagnosed incidentally via CBC showing elevated platelet counts. Symptoms may include **vasomotor symptoms** such as erythromelalgia (burning pain in hands/feet with associated redness and/or warmth), headache, paresthesia, and livedo reticularis. The primary risk is **thrombosis** (venous or arterial). Occasionally, bleeding issues may arise, particularly if platelet counts exceed 1 million due to **acquired von Willebrand syndrome**.
  - **Histology:** Bone marrow shows increased megakaryocytes, reflecting overproduction of platelets.
  - **Genetics:** ET is often associated with **JAK2 V617F**, ***CALR***, or ***MPL* mutations**. *JAK2* mutations are seen in

about 50-60% of cases and are associated with a higher thrombotic risk.
    - **Treatment:** based on **thrombotic risk**:
        - **High risk ET**: History of thrombosis or age >60 with **JAK2 V617F** mutation. Treated with **cytoreductive agents** (e.g., **hydroxyurea**) plus low-dose **aspirin** (if no bleeding). Pregnant patients or those of childbearing potential are treated with **Interferon A** +/- aspirin.
        - **Intermediate risk ET**: Age >60 without JAK2 mutation and no thrombosis history. Treated with low-dose **aspirin** or **hydroxyurea** +/- aspirin.
        - **Low risk ET**: Age ≤60 with **JAK2 V617F** mutation and no thrombosis history. Treated with **aspirin** (81 mg daily).
        - **Very low risk ET**: Age ≤60, no **JAK2 mutation**, and no thrombosis history. Patients are typically observed without treatment. **Aspirin** may be considered if there are no bleeding concerns.
    - **Prognosis:** ET has the best prognosis among myeloproliferative disorders, with a small percentage progressing to post-ET myelofibrosis or leukemia.

- **Primary Myelofibrosis (PMF):**
    - **Clinical Presentation:** a rarer **chronic myeloproliferative neoplasm**, it mostly affects middle-aged and older adults. Patients commonly present with **severe fatigue** and/or **splenomegaly**. Cytopenias are more common than elevated counts.
    - **Histology:** Bone marrow typically shows **fibrosis**, and the marrow space is replaced by fibrous tissue. This leads to bone marrow failure, and blood production often shifts to extramedullary sites like the spleen and liver, but can involve other organs.
    - **Treatment:** largely **supportive**

MYELODYSPLASTIC SYNDROMES (MDS):

MDS is a heterogeneous group of bone marrow disorders classified as **hematologic neoplasms**, characterized by **cytopenias** (anemia, neutropenia, thrombocytopenia). Myelodysplastic syndromes are defined as "primary" or "idiopathic" MDS when there is no antecedent exposure of the patient to something known to carry a risk for developing MDS. Myelodysplastic syndromes are defined as "secondary" when the patient has experienced other treatments known to be associated with development of MDS, such as radiation exposure, radiation therapy, chemotherapy, etc.

- **Clinical Presentation:** Patients are often diagnosed when cytopenias are discovered on routine **CBC** testing, either incidentally or due to symptoms like **fatigue**.
- **Histology:** The bone marrow is typically hypercellular, although some patients may present with hypocellular marrow, and is characterized by **dysplastic hematopoiesis**, including:
    - Abnormal nucleated RBCs
    - **Ringed Sideroblasts (RS)**
    - **Pseudo-Pelger-Huet cells**
    - **Megakaryocytes with abnormal nuclei** (e.g., multiple nuclei instead of the normal single multi-lobated nucleus)
- **Genetics: clonal hematopoiesis** often present with genetic findings, including mutations in ***SF3B1***, ***IDH1/2***, and **del(5q)**, with responses to specific therapies varying based on these mutations.
- **Treatment (FYI ONLY):** Treatment depends on **symptoms** and **genetic findings**:
    - **Erythropoiesis-stimulating agents (ESA)**: Preferred for early MDS patients with isolated symptomatic

anemia and EPO levels ≤500 mU/mL (If EPO level is >500, then ESAs are not likely to be effective and we would treat as we would for MDS with multiple cytopenias as below.

- **Lenalidomide**: Used for patients with low blasts and **del(5q)** if EPO doesn't work/not eligible for EPO.
- **Luspatercept**: Preferred treatment for patients with low blasts and *SF3B1* mutation (often seen with ringed sideroblasts) that is unlikely to respond to an ESA
- **Ivosidenib**: Can be used to treat patients with *IDH1* or *IDH2* mutations
- **Immune suppression therapy (ATG + cyclosporin)**: Considered for patients with features associated with a higher likelihood of responding to immune suppression include age < 60 with < 5% blasts, hypocellular bone marrow, PNH-positive clones, or *STAT3*-mutant T cell clones.
- **Azacitidine**: Used in patients with symptomatic anemia with none of the above features.

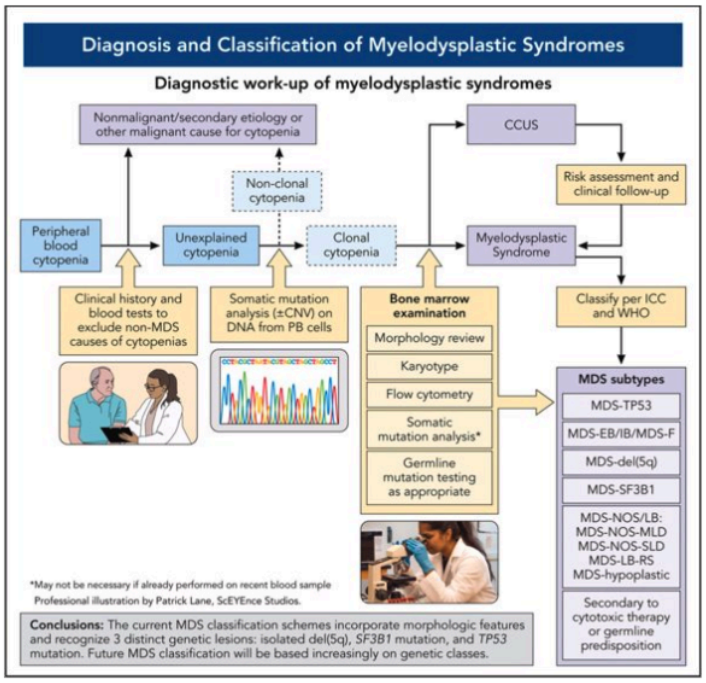


Table 1. Blood tests of potential value in the diagnostic workup of suspected MDS

CBC, including WBC full differential count, red blood cell indices, and reticulocyte count; multiple measurements over time to document persistence/progression of any cytopenia is helpful
RBC-folate/S-folic acid, cobalamin, iron, total iron binding capacity, ferritin, copper, lactate dehydrogenase, bilirubin, haptoglobin, direct antiglobulin test (Coombs test), CRP, alanine transaminase, aspartate transaminase, alkaline phosphatase, albumin, uric acid, creatinine, S-protein electrophoresis (S-immunoglobulins), thyroid function tests, and hemoglobin electrophoresis
Serologic testing to rule out HIV, parvovirus B19 (hypoplastic MDS), cytomegalovirus, hepatitis B, and hepatitis C infections (immunosuppressed patients may require PCR testing for viral infections)
Somatic mutation (and CNV) analysis might be considered to identify clonal hematopoiesis and to inform selection of patient candidates for bone marrow examination
Germ line mutation analysis should be considered in a patient where a suspicion about an inherited bone marrow failure has been raised

CBC, complete blood count; CNV, copy number variation; CRP, C-reactive protein; PCR, polymerase chain reaction; RBC, red blood cell; WBC, white blood cell.

blood® 28 DECEMBER 2023 | VOLUME 142, NUMBER 26

This Chapter's PDF

LINK

- Note: The interactive features of this chapter are not reproducible in this PDF format.