Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Leukemia (Acute and Chronic)

Objectives :

*436 Objectives "437 objectives were not provided"

- Definition
- Historic Perspective
- Etiology and Risk Factors
- Incidence
- Classification
- Comparison of Acute and Chronic Leukemia

Worked on this lecture:

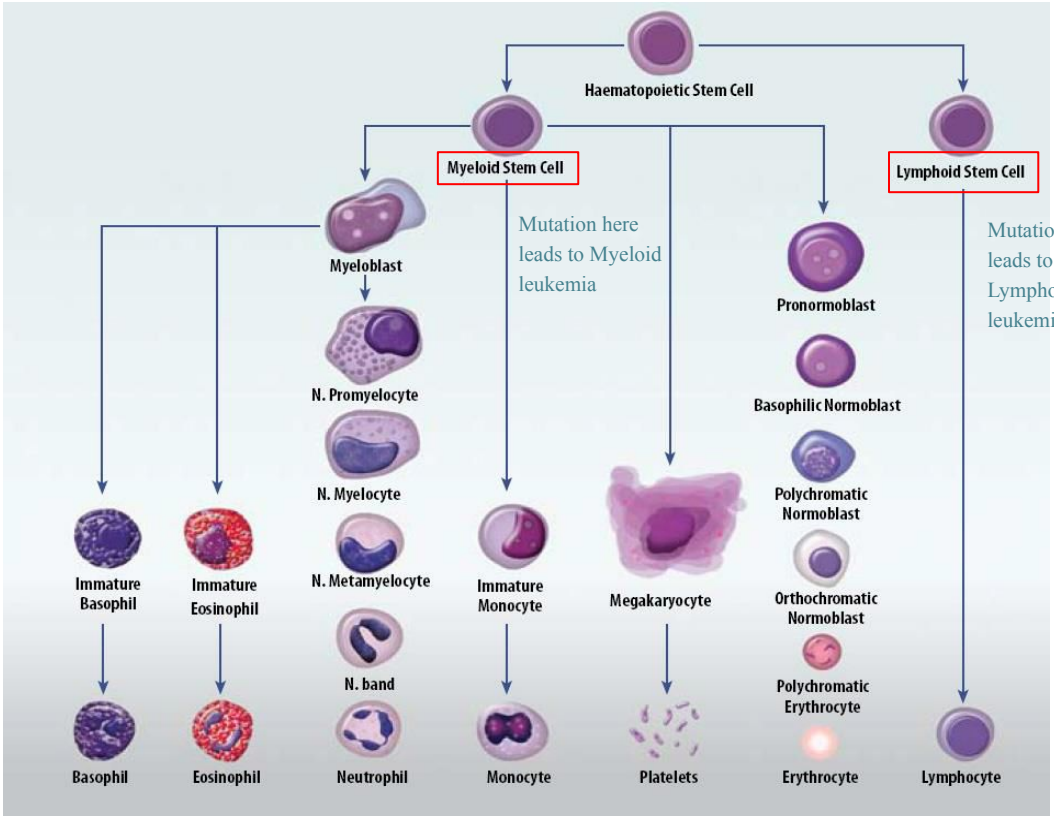
Team leader: AlHanouf AlJaloud
Revised By: Yazeed Aldossare

Resources :

Doctors Slides + Notes: Dr. Ghada ElGohary
Books: Step up, Kumar
Videos: MedEd

Leukemia :

- A group of malignant disorders affecting the blood and blood-forming tissues of
  - Bone marrow
  - Lymph system
  - Spleen
- Neoplastic proliferation of **abnormal WBCs**. As these abnormal WBCs accumulate, they interfere with the production of normal WBCs, as well as the production of erythrocytes and platelets, resulting in anemia and thrombocytopenia.
- Occurs in all age groups
- Results in an **accumulation of dysfunctional cells** because of a **loss of regulation in cell division.** In normal physiology we have controlled cell division "mitosis" and programmed cell death "apoptosis", if these are affected it will lead to excessive cell growth and division which will lead to cancer. Cancer in hematology is in the **stem cells synthesis in the bone marrow** = leukemia.
- Fatal if untreated
  - Progressive



Etiology:

- No single causative agent
- Most from a combination of factors
  - **Genetic** and **environmental influences** Leukemia is not an inherited disease but a +ve family Hx indicates there is a genetic factor.
- Associated with the development of leukemia
  - Chemical agents
  - Chemotherapeutic agents Hx of chemotherapy or radiation
  - Radiation
  - Viruses
  - Immunologic deficiencies
  - Down's syndrome

Classification of leukemias:

- Two major types acute and chronic, and (4 subtypes) of leukemias
  - **Acute leukemias**
    - Acute lymphoblastic leukemia (ALL)
    - Acute myelo*genous* leukemia (AML) (also "myeloid" or "nonlymphocytic")
  - **Chronic leukemias**
    - Chronic lymphocytic leukemia (CLL)
    - Chronic myel*oid* leukemia (CML)

  (Within these main categories, there are typically several subcategories)

Acute versus chronic:

	Acute	Chronic
Cell maturity	Clonal proliferation of **immature** hematopoietic cells (the formation of blood or blood cells)	**mature** forms of WBC; onset is more gradual
Nature of disease onset	More aggressive Poorly differentiated blast immature population	Less aggressive Well differentiated cell population
	Rapidly fatal outcome, if untreated	Associated with longer survival, even if left untreated

Two-hit model of leukemogenesis:

A) Loss of function of transcription factors needed for differentiation:

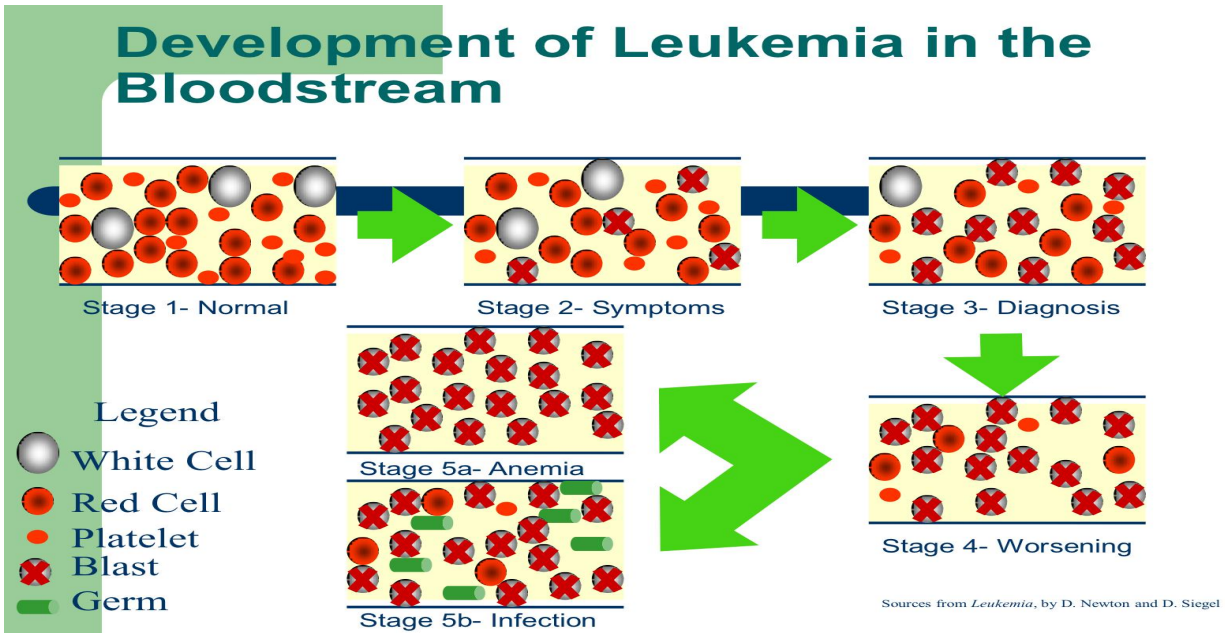
- eg. AML1-ETO, CBFb-SMMH, PML-RARα genetic translocation t(15;17) which leads to> acute promyelocytic leukemia M3 associated with DIC (Bleeding disorder)

B) Gain of function mutations of tyrosine kinases:

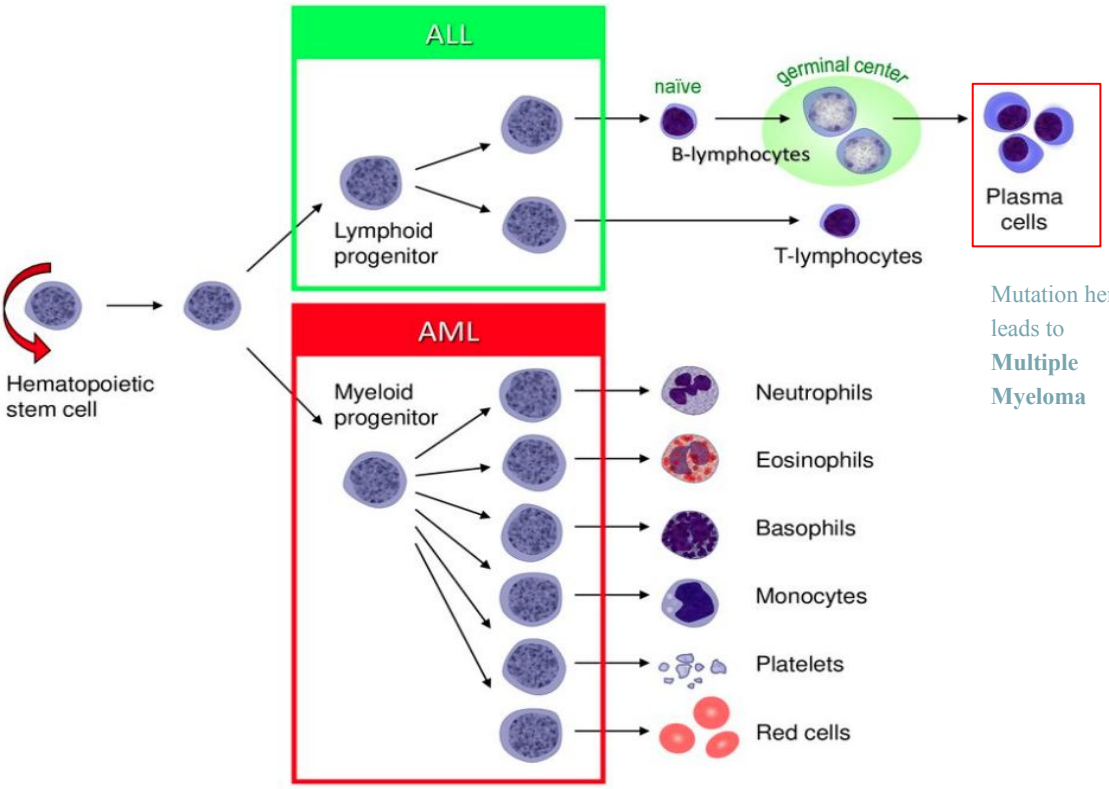
- eg. FLT3, c-KIT mutations N- and K-RAS mutations BCR-ABL (9,22) TEL-PDGFbR

Differentiation block + Enhanced proliferation

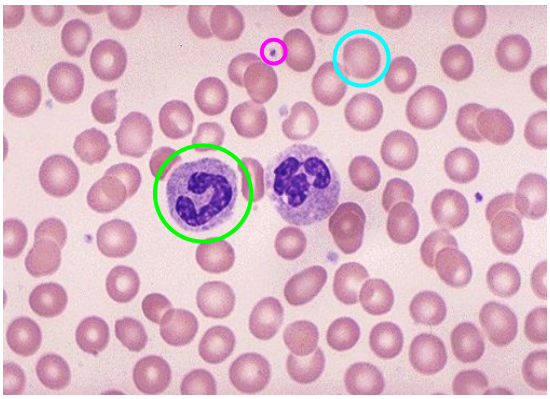
Acute Leukemia



Best prognosis is when diagnosed by stage 3 or prior

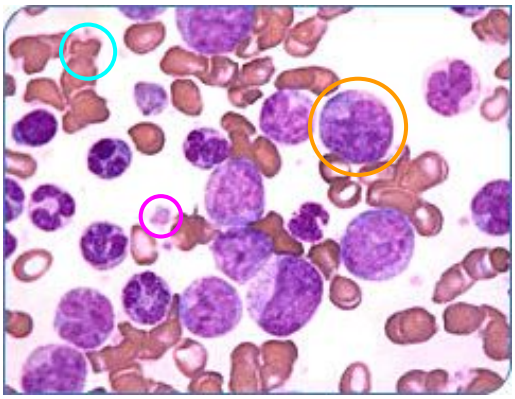


Mutation here leads to **Multiple Myeloma**



Normal human blood

Normal shape and count



Blood with leukemia Abnormal proliferation

- Platelet (Immature platelets "Megakaryocytes" in leukemia)
- Red Cell
- White Cell
- Blasts

Clinical Manifestations of leukemia:

Relate to problems caused by:

Bone marrow failure

- Overcrowding by abnormal cells
- Inadequate production of normal marrow elements
- Anemia, thrombocytopenia, ↓ number and function of WBCs Leading to ↑ incidence of infection.

Leukemic cells infiltrate patient's organs:

- Splenomegaly
- Hepatomegaly
- Lymphadenopathy
- Bone pain, meningeal irritation, oral lesions (chloromas) Mostly with acute

In generale leukemia share the same symptoms the difference is the the severity and onset. Acute leukemia symptoms develop within days, whereas Chronic take many years and are usually asymptomatic at the time of the diagnosis, and the findings might be incidental. Patient with chronic leukemia might have constitutional symptoms "especially in CML" weight loss, fatigue.. Etc, and some signs of anemia, ↑infection ...etc but not severe enough to require ER visit.

Myelogenous Leukemia:

Leukemia characterized by proliferation of **myeloid tissue** (as of the **bone marrow** and **spleen**) and an a**bnormal increase in the number** of granulocytes, myelocytes, and myeloblasts in the circulating blood.

- **Myeloid tissue:**
  Is a **biologic tissue** with the ability to perform **hematopoiesis**. It is mainly found as the **red bone marrow in bones**, and is often synonymous with this. However, myeloid can also be present in the **liver** and **spleen** .
- **Myelocyte:**
  Is a **young cell of the granulocytic** series, occurring normally in **bone marrow**, but not in circulating **blood** (except when caused by certain diseases).
- **Granulocytes:**
  Are a category of **white blood cells** characterized by the presence of **granules** in their **cytoplasm**.They are also called polymorphonuclear leukocytes (PMN or PML) because of the varying shapes of the **nucleus**, which is usually lobed into three segments.
- **Myeloblast:**
  Is a unipotent stem cell, which will differentiate into one of the actors of the **granular** series.

Acute Leukemias

Acute Myelogenous Leukemia (AML)

- Leukemia characterized by proliferation of **myeloid** tissue (as of the bone marrow and spleen) and an abnormal increase in the number of **granulocytes**, **myelocytes**, and **myeloblasts** in the circulating blood
- One fourth of all leukemias
  - 85% of the acute leukemias in adults M > F Exposure to Benzene, Radiation play a major role.
- Abrupt, dramatic onset
  - Serious infections, abnormal bleeding
- Uncontrolled proliferation of myeloblasts
  - Hyperplasia of bone marrow and spleen
- Curable in minority of adults
- Important AML variant is Acute promyelocytic leukemia **(M3)**:
  - characterized by **t(15;17)** PML-RARα "**P**ro**M**yelocytic **L**eukemia-**R**etinoic **A**cid **R**eceptor **α**"
  - Associated with DIC
  - Presence of Auer rods
  - treated with All-Trans retinoic acid "Vit A" with concurrent chemotherapy

Acute Lymphocytic Leukemia (ALL)

- Most common type of leukemia in children M > F
- 15% of acute leukemia in adults
- Immature lymphocytes proliferate in the bone marrow
- Signs and symptoms may appear abruptly
  - Fever, bleeding
- Insidious with progressive:
  - Weakness, fatigue signs of anemia
- Central nervous system manifestations. Must give CNS prophylaxis! **"Prophylactic intrathecal drugs such as methotrexate"**
- Curable in 70% of children, and only in minority of adults

Clinical presentation: Of **acute** anemia both ALL & AML

Will present with sign or symptoms related to:

- Pancytopenia:
  - ↓ WBC → Infection. E.g Pneumonia, UTI
  - ↓ Hb → Anemia. Dyspnea, Pallor, fatigue
  - ↓ Platelets (thrombocytopenia)→ Bleeding. Epistaxis, easily bruised, petechiae
- Organ infiltration:
  - Lymphadenopathy, Splenomegaly, Hepatomegaly.
- CNS: almost always in acute lymphocytic anemia
  - 5-10% of patient with **ALL**
  - Squint, Blurred vision, Headache.

Chronic Leukemias

Chronic Myelogenous Leukemia (CML)

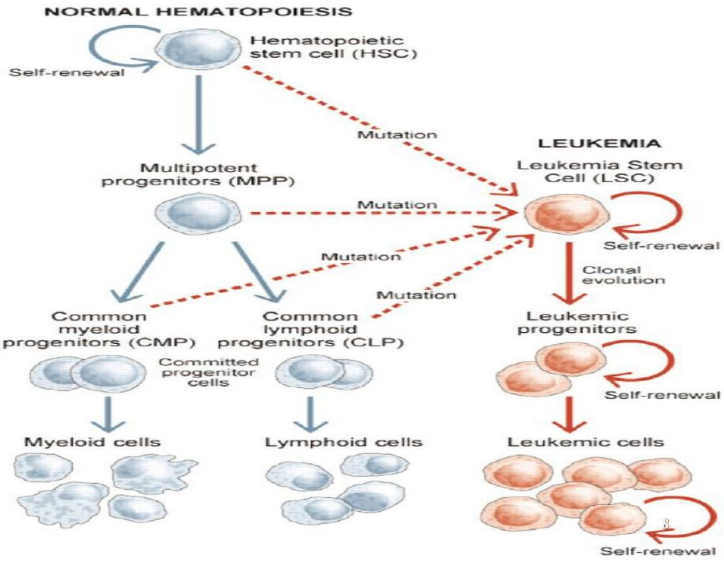
- Excessive development of **mature** neoplastic granulocytes in the bone marrow:
  → Move into the peripheral blood in massive numbers
  → Ultimately infiltrate the liver and spleen
- Philadelphia chromosome
  - Genetic marker. The chromosome abnormality that causes chronic myeloid leukemia (CML) (9 & 22) "BCR-ABL"
  - It has **tyrosine kinase activity** and enhanced phosphorylation that result in altered cell growth
  - That's why we treat it with oral tyrosine kinase inhibitors "**Imatinib** first line treatment in chronic phase"
- Chronic, stable phase for many years followed by **acute, aggressive (blastic** Immature**) phase** (Blast crisis) end stage of the disease.
- Massive splenomegaly is characteristic.

Chronic Lymphocytic Leukemia (CLL)

- disease of the old age >65
- Production and accumulation of **functionally inactive** but long-lived, **mature**-appearing lymphocytes
- B cell involvement
- Lymph node enlargement is noticeable throughout the body
  - ↑ incidence of infection
- Complications from early-stage CLL is rare
  - May develop as the disease advances
  - Pain, paralysis from enlarged lymph nodes causing pressure.

Hairy Cell Leukemia :

- Subtype of CLL
- 2% of all adult leukemias
- Usually in males > 40 years old
- Chronic disease of lymphoproliferation
- B lymphocytes cells that have a **"hairy" appearance** and infiltrate the bone marrow and liver Can be Dx by blood morphology
- Symptoms from
  - Splenomegaly, Pancytopenia, Infection, Vasculitis production of autoantibodies that attack normal blood vessels → Autoimmune thrombocytopenia, **Autoimmune hemolytic anemia**
- Treatment
  - Alpha-interferon, Pentostatin, Cladribine



Unclassified Leukemias:

Most aggressive and has worst prognosis

- Subtype cannot be identified
- Malignant leukemic cells may have
  - Lymphoid, myeloid, or mixed characteristics.
- Frequently these patients do not respond well to treatment
  - Poor prognosis.

Differential Diagnosis:

1. Aplastic anemia
   - Autoimmune disease which cause complete deficiency of all types of blood cells
2. Myelodysplastic syndromes
3. Multiple myeloma
   - Malignancy in the plasma cells, leads to pancytopenia
4. Lymphomas
   - Malignancy in the lymph nodes
5. Severe megaloblastic anemia
   - Vitamin B12 deficiency *Extra "**Pernicious anemia**: diminished intrinsic factors → ↓B12 absorption → megaloblastic anemia"
6. Leukemoid reaction Neutrophilia; mostly in septicemia
   - How to to know benign leukemoid reaction from leukemia? *Extra from book
     i. No splenomegaly
     ii. History of precipitating event e.g., **infection**
     iii. ↑Leukocyte alkaline phosphatase

Diagnostic Studies Earlier Dx = Better prognosis

- To diagnose and classify To know if Lymphoid or Myeloid
  - **Peripheral blood evaluation**
    - CBC
      - WBC count:
        - Acute: might be normal, decrease or **elevated**.
        - Chronic: mostly **elevated**
      - ↓Hg "Anemia"
      - ↓platelets "Thrombocytopenia"
    - Blood smear
      - If **acute** it must show Blasts " You may see blast in chronic leukemia but it should not exceeds 5%"
      - **CLL**: Smudge cells -- fragile leukemic cells that ruptures when placed on glass slide.
  - **Bone marrow evaluation** by biopsy Required for Dx
    - **ALL**:
      - >20% Blasts of lymphoid lineage
      - +ve c**ALL**a, +ve Tdt
    - **AML**:
      - >20% Blasts of myeloid lineage
      - Auer rods if APL
      - **+ve myeloperoxidase**
  - Flow cytometry
    - Shows the receptors in each cell to know the clonality and **determine whether Myeloid or Lymphoid**
- To identify cell subtype and stage
  - Morphologic, histochemical, immunologic, and "**cytogenetic method** To know the prognosis"

Collaborative Care Treatment

- Goal is to **attain remission** (when there is no longer evidence of cancer cells in the body)
  - **What is remission?**
    - The main aim of treatment for acute lymphoblastic leukaemia is to give a remission. This means that the abnormal, immature white cells or blasts can no longer be detected in the blood or bone marrow, and normal bone marrow has developed again.
    - For many people with acute lymphoblastic leukaemia the remission lasts indefinitely and the person is said to be cured.

- Treatment of leukemia "especially acute" starts by **treating emergencies first**:
  - **Antibiotic**: as necessary for **infection**.
  - **Blood transfusion:** as necessary for **anemia**
  - **Platelet transfusion**: as necessary for **bleeding**

- **Chemotherapeutic treatment:**

A) Induction therapy
- Attempt to induce or bring remission
- Seeks to destroy leukemic cells in the tissues, peripheral blood, bone marrow
- Patient may become critically ill
- Provide psychological support as well

B) Intensification therapy
- High-dose therapy
- May be given after induction therapy
- Same drugs at higher doses and/or other drugs

C) Consolidation therapy
- Started after remission is achieved you must give consolidation therapy after induction Tx to avoid recurrence
- Purpose is to eliminate remaining Leukemic cells that may not be evident

D) Maintenance therapy
- Lower doses of the same drug

- **Chemotherapy Regimens**
    - Combination chemotherapy
        - Mainstay treatment
        - 3 purposes
            - ↓ drug resistance
            - ↓ drug toxicity to the patient by using multiple drugs with varying toxicities
            - Interrupt cell growth at multiple points in the cell cycle

- **Bone Marrow and Stem Cell Transplantation**
    - **Goal:** Totally eliminate leukemic cells from the body using combinations of chemotherapy with or without total body irradiation
    - Eradicates patient's hematopoietic stem cells, replaced with those of an **HLA-matched** (Human Leukocyte Antigen)
        - Sibling (is a brother or a sister; that is, any person who shares at least one of the same parents)
        - Volunteer
        - Identical twin
        - Patient's own stem cells removed before
        - Parent's

Case:

- 17 years lady presented to the ER with CBC: WBCs 50,000 HGB 10 PLT 15000
- Abnormal circulating blasts 30% More Hx must be taken first!.

- **Hx:**
  - Patient presented with 10 Days of fever, diffuse erythematous skin rash, difficulty breathing, inability to do hard effort, blurred vision.
- **PE:**
  - Hepatosplenomegaly, axillary lymphadenopathy.

From the abrupt presentation, short onset and the presence of blasts you know it is **acute leukemia**. You can't tell whether lymphoid or myeloid **unless you do a bone marrow biopsy.**

- **How to proceed with Diagnosis and Management?**
  - Bone marrow biopsy and flow cytometry
    - for diagnosis and to determine whether lymphoid or myeloid
  - Cytogenetic test
    - To know the prognosis
- According to the results you will manage

- **Diagnosis and Risk stratification:**

1) Peripheral blood morphology
   - Abnormal **blasts**
2) Peripheral blood flow cytometry to show clonality
   - **30 % blasts** with **CD33** Myeloid specific receptor, CD34 +ve
3) BMBx for
   - Morphology (**myeloblasts**)
   - Cytogenetics for prognosis **t(8:21)** Acute myeloid leukemia translocation
   - Flow cytometry (**50% blasts** express M antigens)
   - Molecular (FLT3 –ITD +ve)

The results shows it is **Acute Myeloid Leukemia**

- **Treatment:**
  - **Goals:**
    1) Remission induction (chemo for 28 days)
    2) Response assessment (Day 28)
    3) Consolidation (chemo / SCT stem cell transplant)
    4) Maintenance. But if the patient is high risk consider stem cell transplant

summary:

<table>
<tr><td></td><td colspan="4">Leukemia
• Neoplastic proliferation of abnormal WBCs that interfere with the production of normal WBCs, as well as the production of erythrocytes and platelets, resulting in ↑infection anemia and thrombocytopenia.</td></tr>
<tr><td></td><td colspan="2">Acute</td><td colspan="2">Chronic</td></tr>
<tr><td rowspan="2">Type of cells</td><td colspan="2">Blasts cells</td><td colspan="2">Mature cells</td></tr>
<tr><td>Lymphoid</td><td>Myeloid</td><td>Lymphoid</td><td>Myeloid</td></tr>
<tr><td>Age</td><td>Children</td><td>Adults</td><td>Old age >65</td><td>Adults</td></tr>
<tr><td>Onset</td><td colspan="2">Abrupt symptoms within days</td><td colspan="2">Asymptomatic for years</td></tr>
<tr><td>Symptoms include:</td><td colspan="4">Anemia, thrombocytopenia, ↓ number and function of WBCs Leading to ↑ incidence of infection. Splenomegaly, Hepatomegaly, Lymphadenopathy, Bone pain</td></tr>
<tr><td>General</td><td>Most common type in children
CNS manifestation.
Must prophylax the CNS with intrathecal methotrexate.</td><td>Acute promyelocytic anemia M3 is an important variant of AML characterized by: PML-RARα, DIC, Auer rods.
Treated with All-trans retinoic acid.</td><td>Presence of Smudge cell in BMB.
Hairy cell leukemia a variant of CLL
Characterized by B lymphocytes that have a hairy cell appearance, symptoms induced vasculitis. Results in Autoimmune hemolytic anemia, treated with cladribine</td><td>Chronic phase for many years followed by acute phase called blast crisis
Philadelphia chromosom as a genetic marker, t(9;22), BCR-ABL
Treated with oral tyrosine kinase inhibitor Imatinib.</td></tr>
<tr><td>Diagnosis</td><td colspan="4">• Peripheral blood evaluation (Count + Smear)
• Bone marrow biopsy
• Flow cytometry To differentiate between Myeloid and lymphoid
• Cytogenetic To know the prognosis</td></tr>
<tr><td>Treatment</td><td colspan="4">1. Emergencies treatment (Antibiotic, blood transfusion, platelets ..etc)
2. Chemotherapy
3. Consolidation therapy
4. Maintenance or SCT</td></tr>
</table>

Questions

1. A **34-year**-old man is evaluated for a **3-month history** of **fatigue**, **early satiety**, and a 10-kg **weight loss**.
On physical examination:
No lymphadenopathy is noted. The spleen is **palpable** 10 cm below the costal margin.
Laboratory studies:
   - Hemoglobin level of 8.4 g/dL
   - leukocyte count of 314,000/µL
   - platelet count of 622,000/µL.

A peripheral blood smear is show **myelocytes**. Which of the following is the most likely genetic mutation to explain this patient's findings?

A) BCR-ABL
B) IGH/CD1
C) JAK2 V617F
D) PML-RARα

Correct Answer: A
Patients with suspected chronic myeloid leukemia should be tested for an underlying BCR-ABL mutation. He has the classic presentation for CML with the insidious onset of fatigue; early satiety and progressive weight loss associated with splenomegaly.

2. A **43-year**-old woman is admitted to the hospital for **fatigue** of **4 weeks' duration**, **easy bruising** and **bleeding gums** of **1 week's duration**, and a **1- day fever**.
On physical examination:
the patient appears. multiple **ecchymoses** and **petechiae**. **Hepatomegaly** is also noted. .
Laboratory studies:
   - Leukocyte count 32,000/µL
   - Platelet count 25,000/µL
   - Prothrombin time 24 s

A peripheral blood smear shows **80% immature blasts** with prominent **Auer rods**. Which of the following is the most appropriate initial management?

A) t (9;22) testing
B) Chemotherapy
C) All-trans retinoic acid
D) t (15;17) testing

Correct Answer: C
Treat **Acute promyelocytic leukemia.** ATRA should be initiated without waiting for confirmation as long as the presentation strongly suggest APL. that's why the answer is not D

3. A **56 year** old man presents to hospital with abdominal discomfort and is found to have **splenomegaly** and an abnormal full blood count. In CML, which of the following statements is correct?

   A. Allogeneic stem cell transplantation remains the first -choice therapy in chronic phase
   B. At presentation a majority of white cells are blast cells
   C. t(15;17) translocation
   D. The Philadelphia (Ph) chromosome t(9;22) is present.

   Correct Answer: D

4. A **5-year**-old girl presents with her parents who have become concerned about the small **petechiae** and **ecchymoses** on her skin. An abdominal examination reveals **hepatosplenomegaly**. You suspect an acute leukaemia. The most appropriate initial investigation for diagnosis is:

   A. A Chromosomal analysis of bone marrow cells.
   B. Cytochemical analysis of bone marrow cells
   C. Direct microscopy of bone marrow cells
   D. Electron microscopy
   E. Flow cytometry.

   Correct Answer: C
   In order to diagnose an acute leukaemia, defined as ≥20% blasts in bone marrow, an examination of a bone marrow aspirate under microscopy (C) is necessary. Flow cytometry (E) is useful in distinguishing AML from ALL. Electron microscopy (D) has a reduced role with advanced immunotyping techniques available. (A) and (B) are useful investigations and prognosis once a leukaemia is confirmed.

5. A **65-year**-old man presents to you reporting he has become increasingly worried about his **lack of energy in the last 2 weeks**. He mentions he has been increasingly **tired**, **sleeping for long periods** and has suffered from **fevers** unresponsive to paracetamol. He became increasingly worried when he noticed **bleeding originating from his gums**. His blood film shows **auer rods**. The most likely diagnosis is:

   A. Acute lymphoblastic leukaemia
   B. Chronic Myeloid leukaemia
   C. Disseminated intravascular coagulation
   D. Acute myeloid leukaemia
   E. Chronic lymphoblastic leukaemia

   Correct Answer: D
   Presentation is acute, Auer rods presents in Acute promyelocytic leukemia which is a subtype of Acute myeloid leukemia.

6. A **29-year**-old woman complains of **tiredness**, especially during activity. On examination the patient appears pale. **Auer rods** can be seen on peripheral blood smear. The patient is referred for a bone marrow biopsy and the extracted cells are sent for cytogenetic analysis. The most likely results are:

   A. t(8:21)
   B. t(15;17)
   C. t(9:22)
   D. Philadelphia chromosome
   E. BCR-ABL

   Correct Answer: B
   This patient is suffering from an acute promyelocytic leukaemia, a subtype (M3) of AML. It is due to t(15;17) translocation. The t(8;21) abnormality part of the acute myelogenous leukaemia disorders (M2 variant). The t(9;22) (C) translocation occurs in CML associated with the Philadelphia chromosome with BCR-ABL marker.

7. A **70-year-old** woman complains of **tiredness**, **fatigue** and **weight loss**. Blood tests reveal an **elevated WBC** and on examination **splenomegaly** is palpated. Cytogenetics are positive for the **Philadelphia chromosome** and the patient is diagnosed with chronic myeloid leukaemia. The most appropriate treatment is:

   A. Chemotherapy
   B. Imatinib
   C. Stem cell transplant
   D. Venesection

   Correct Answer: B
   Chronic myeloid leukaemia occurs due to the reciprocal translocation of the Philadelphia chromosome t(9;22) BCR-ABL, which has uncontrolled tyrosine kinase activity. Treatment begins with imatinib a tyrosine kinase inhibitor which blocks the activity of BCR/ABL.

8. A 56 years old man presented to the clinic with abdominal pain. Abdominal examination revealed splenomegaly. CBC is showing marked leukocytosis of 145.000 cells/ul, Hemoglobin 11 /dl, Platelets 400.000 /ul. Peripheral blood molecular testing for BCR/ABL is positive. Which ONE of the following is the most likely diagnosis?

   A) Acute Lymphocytic Leukemia
   B) Acute Myeloid Leukemia
   C) Chronic Lymphocytic Leukemia
   D) Chronic Myeloid Leukemia

   Correct Answer: D