"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all." – William Osler

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MEDICINE
TEAMWORK

LEUKEMIA

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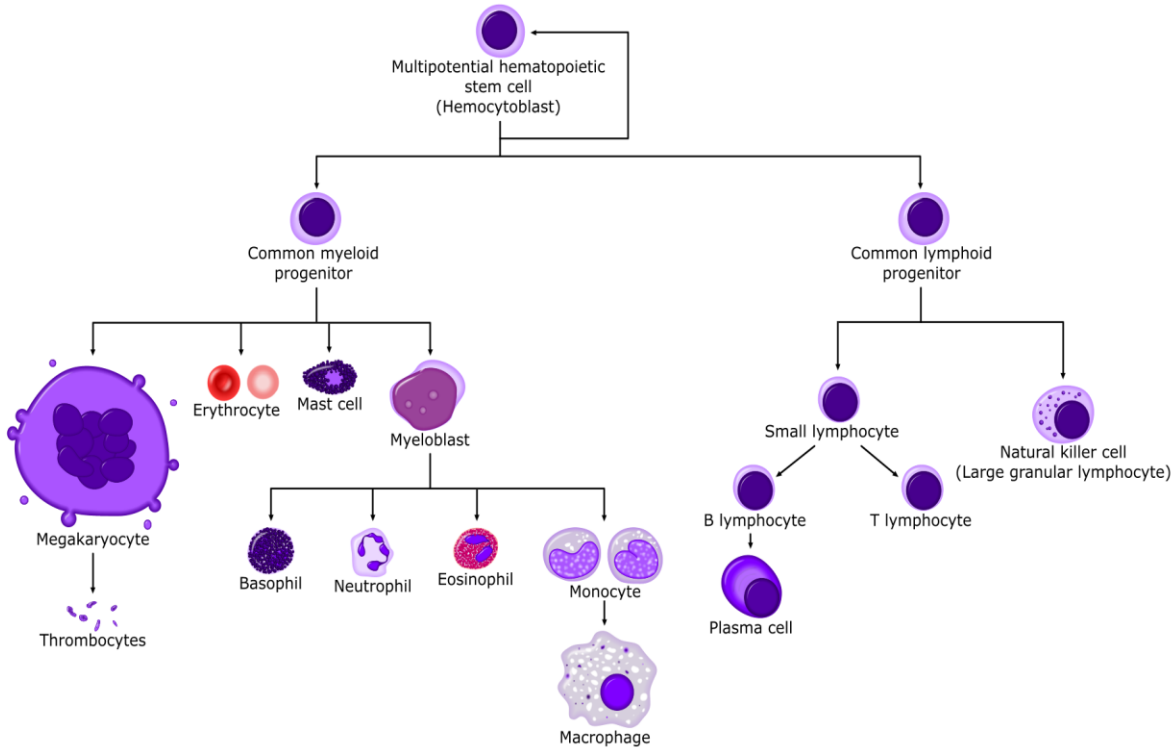
Leukemia

Hematopoietic system



In normal hemostasis multipotenential hematopoietuc stem cells (Hemocytoblasts) differentiate into:

- Common Myloid Progenitors (Producing Erythrocytes, mast cells, myeloblasts…etc)
- Common Lymphoid Progenitors (Further differentiating into B-Lymphocytes, T-Lymphocytes and Natural Killer Cells.

From the names of these two types of progenitor cells we can classify Leukemia based on origin and whether it's Acute or Chronic

- This gives us four types:
  - Acute Myelogenous/ Myeloblastic Leukemia
  - Acute Lymphoblastic Leukemia
  - Chronic Myelogenous/Myeloid Leukemia
  - Chronic Lymphocytic Leukemia

Definition

Leukemia is an accumulation of white cells in the circulation due to increased production and/or reduced clearance

Acute Leukemia

Acute leukemia is mainly due to proliferation and accumulation of **immature** cells due to maturation arrest at certain stage of differentiation

Acute Leukemia → Immature Cells
Chronic Leukemia → Mature Cells

Chronic Leukemia

Chronic leukemia is mainly due to proliferation and accumulation of **mature** cells and reduced apoptosis (programmed cell death)

Sub-classification Acute Myelogenous Leukemia (AML)	Sub-classification Acute Lymphoblastic Leukemia (ALL)
• M0 : myelobalsts with minimal differentiation • M1 : myelobalsts without maturation • M2: myelobalsts with some maturation • M3: Promyelocytes • M4: myelomonocytic • M5: meyloblastic • M6: erythroblastic • M7:megakaryocytic	• **L1: Childhood ALL** • **L2: Adulthood ALL** • **L3: Burkett's type ALL**

- Leukemia is sub-classified based on morphology.
- M3 → Associated with DIC (Disseminated intravascular coagulation)
- M4/M5 → Cause Gum Hypertrophy.
- 80-90% of adult leukemias are AMLs
- 90% of childhood leukemias are ALLs
- AML can be differentiated from ALL by the presence of Auer Rodes (formed by the aggregation of myeloid granules)
- Over all, Acute Leukemias are caused by unregulated proliferation of immune cells incapable of further differentiation (Blasts) → Leading to marrow replacement and hematopoietic failure (Reduction in RBC, WBC and Platelet production)→ thus leading to the complications of leukemia (Anemia, infections and bleeding).
- ALL is more responsive to therapy

- The causes of leukemia are largely unknown.
- The incidence of leukemia among persons who have been exposed to high levels of radiation is unusually high.
- An increased incidence of leukemia also is associated with exposure to benzene and the use of antitumor drugs (*i.e.,* mechlorethamine, procarbazine, cyclophosphamide, chloramphenicol, and the epipodophyllotoxins).
- Leukemia may occur as a second cancer after aggressive chemotherapy for other cancers, such as Hodgkin's disease.
- The existence of a genetic predisposition to develop acute leukemia is suggested by the increased leukemia incidence among a number of congenital disorders, including Down syndrome, von Reckinghausen's disease, and Fanconi's anemia.
- In individuals with Down syndrome, the incidence of acute leukemia is 10 times that of the general population.
- Also, there are numerous reports of multiple cases of acute leukemia occurring within the same family.
- Some T-cell leukemias, hairy cell leukemia, and lymphoma are caused by retroviruses, HTLV-1 and HTLV-2

Presentation of Acute Leukemia

Due to rapid proliferation of abnormal cells and occupation of bone marrow with these cells, there is progressive reduction of normal white cells, red cells and platelets.

Patients present with:

- Anemia → fatigue, weakness, headache, poor appetite and pallor.
- Thrombocytopenia → bruises, bleeding tendency.
- Neutropenia→ fever, infection.

- Thrombocytopenia → A decrease in Blood Platelets
- Neutropenia → A decrease in WBCs

Manifestations:
Although ALL and AML are distinct disorders, they typically present with similar clinical features.
The warning signs and symptoms of acute leukemia are fatigue, pallor, weight loss, repeated infections, easy bruising, nosebleeds, and other types of hemorrhage.

Laboratory Diagnosis

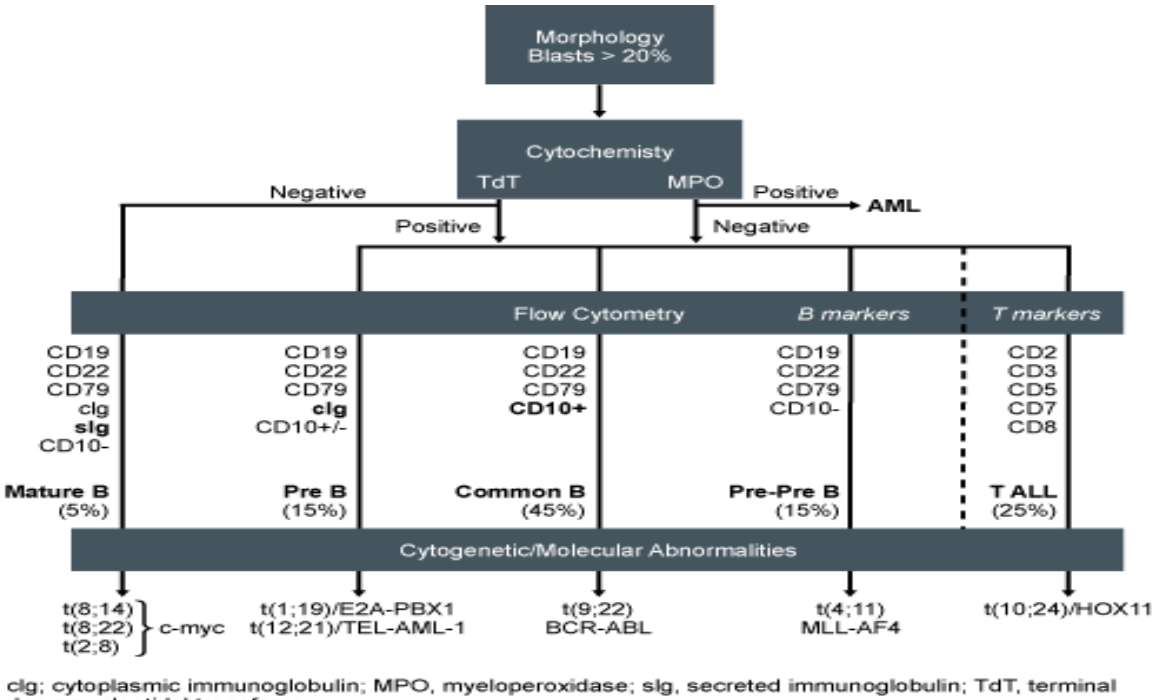
- Leukocytosis
- Anemia
- Thrombocytopenia
- Blasts in peripheral blood film and bone marrow
- Cytochemistry (special stains)
- Flowcytometry
- Chromosomal/ cytogenetic tests

- Acute Leukemia is identified morphologically by the presence of Blasts
- However we can only tell the type via Flow Cytometry
- ALL → Burket's type → Vacuoles are present around the margins of Blasts.

Bone Marrow Aspirate

- Biopsy the bone to look at its architecture because sometimes (in Lymphomas for example) there is no change in cells, but depositions will be found on bone.

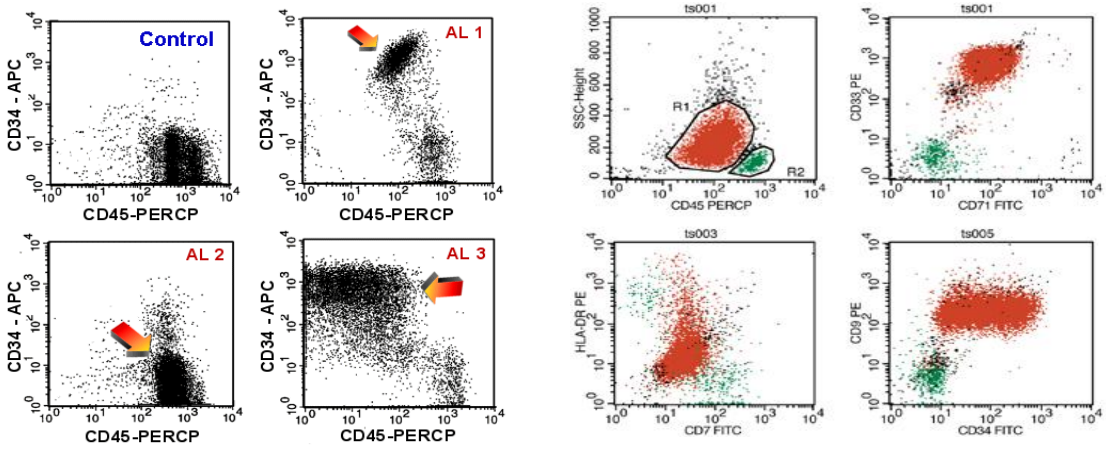
Flowcytometry



cIg; cytoplasmic immunoglobulin; MPO, myeloperoxidase; sIg, secreted immunoglobulin; TdT, terminal deoxynucleotidyl transferase

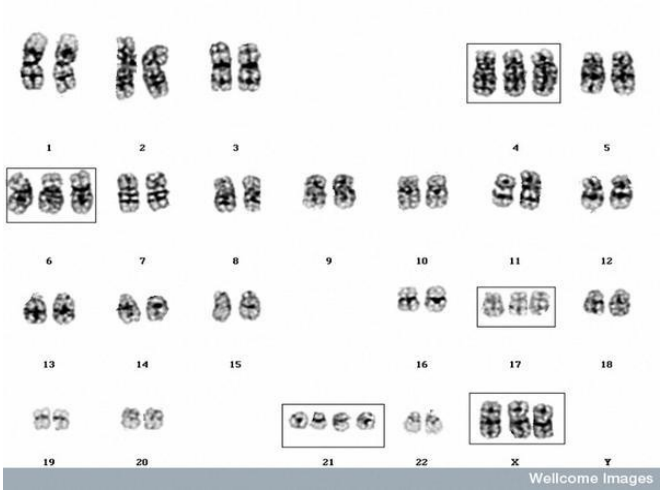
In Cytochemistry
Monocytic Leukemia (AML) → Non-Specific Esterase is used for identification

Flowcytometry



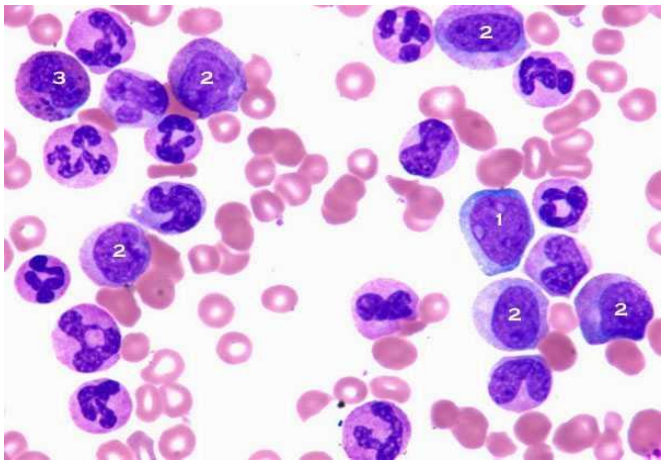
In Flowcytometry:
Notice the pattern and differentiation
CD = Cluster Differentiation

Chromosomal analysis

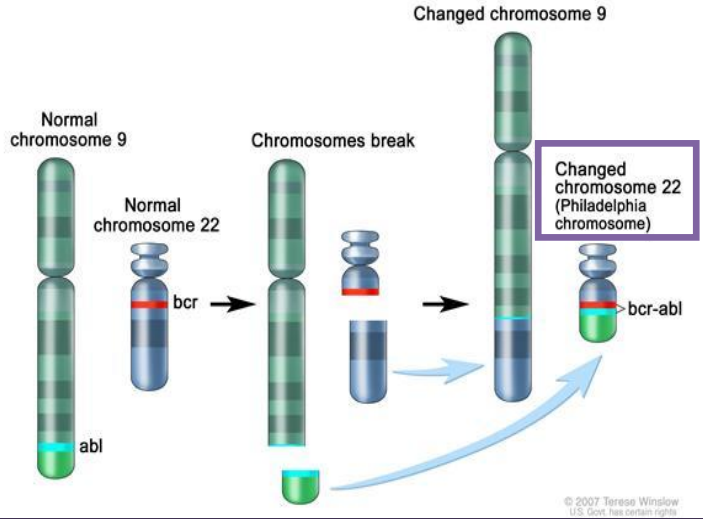


Important for
Classification and prognosis

CML



Usually discovered late
Patients present with Splenomegally



- Bcr is a naturally present gene
- Abl is an Oncogene
- Oncogene = A gene that in certain circumstances transforms a cell into a tumor cell.
- In normal circumstances they cause no harm, but when translocation occurs and they fuse (BCR-ABL), production of Tyrosine Kinase occurs, leading to an increase in Neutrophil and Platelet production.

Table 1. Fusion transcripts detected by Signature® LTx v2.0 Kit

Classification	Translocations	Fusion Transcripts
CML	t(9;22)	BCR/ABL1 (b2a2)
		BCR/ABL1 (b3a2)
ALL	t(9;22)	BCR/ABL1 (e1a2)
	t(1;19)	E2A/PBX1 (e13/e2)
	t(12;21)	TEL/AML1 (e5/e2)
	t(4;11)†	MLL/AF4 (e9/e5)
		MLL/AF4 (e10/e4)
APL	t(15;17)	PML/RARα (L form)
		PML/RARα (S form)
AML	Inv16	CBFB/MYH11 (A type)
		CBFB/MYH11 (D type)
	t(8;21)	AML1/ETO (e5/e12)

†*Signature® LTx v2.0 Kit can detect two t(4;11) fusion transcripts (e10/e4) and (e9/e5), but does not discriminate between them.*

Chronic Leukemia:

- In contrast to acute leukemias, chronic leukemias are malignancies involving the proliferation of well-differentiated myeloid and lymphoid cells.
- The two major types of chronic leukemia are chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML).
- Men are affected twice as frequently as women.
- CML accounts for 15% of all leukemias in adults. It is predominantly a disorder of adults between the ages of 30 and 50 years, but it can affect children as well.
- The incidence is slightly higher in men than women.

CLL

- CLL typically follows a slow and indolent course.
- The clinical signs and symptoms are largely related to the progressive infiltration of neoplastic lymphocytes in the bone marrow and extramedullary tissue and to secondary immunologic defects.
- Often affected persons are asymptomatic at the time of diagnosis, and lymphocytosis is noted on a complete blood count obtained for another, unrelated disorder.
- Fatigue, reduced exercise tolerance, enlargement of superficial lymph nodes, or splenomegaly usually reflects a more advanced stage.
- CLL is the least aggressive type of leukemia

CML

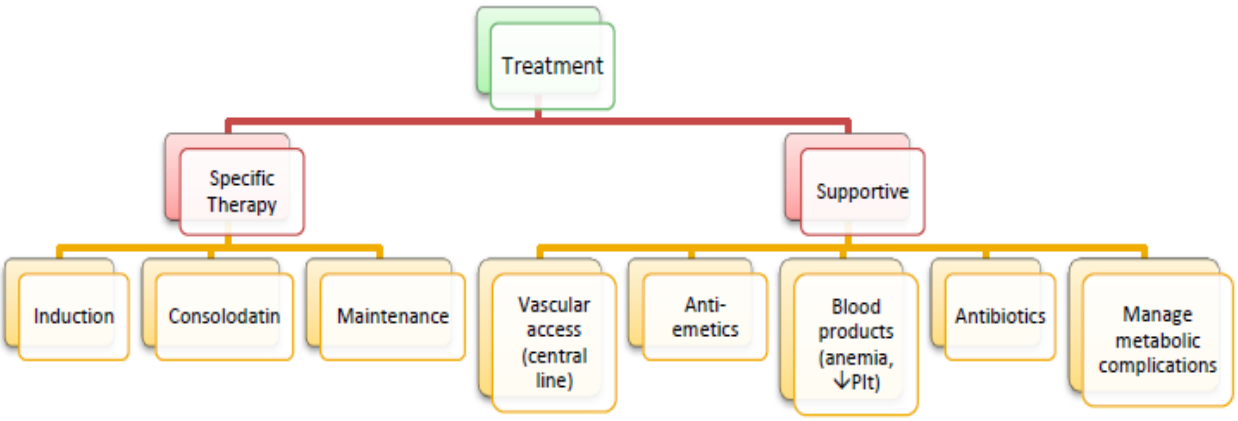
- Typically, CML follows a triphasic course
  - (1) a chronic phase of variable length
  - (2) a short accelerated phase
  - (3) a terminal blast crisis phase.
- The onset of the chronic phase is usually slow with nonspecific symptoms such as weakness and weight loss.
- The most characteristic laboratory finding at the time of presentation is leukocytosis with immature granulocyte cell types in the peripheral blood.
- Anemia and, eventually, thrombocytopenia develop.
- Anemia causes weakness, easy fatigability, and exertional dyspnea.
- Splenomegaly is often present at the time of diagnosis; hepatomegaly is less common; and lymphadenopathy is relatively uncommon.
- Mostly in adults ages 30-50

Treatment of Acute Leukemia

- Supportive: RBC, & Platelet transfusion
- Single room
- Reverse isolation
- Antibiotic and antifungal prophylaxis,
- Chemotherapy: induction, consolidation, maintenance
- G-CSF as indicated

Overall, treatment aims at reducing number of Blasts to an undetectable level and restoring hematopoiesis

1. 1-Treatment in emergencies:
   a. Antibiotics for infections
   b. Blood transfusions
2. 2- Aggressive chemotherapy followed by maintenance therapy
3. 3- Bone marrow transplantation



Specific Therapy (Acute Laukemia)

1. Induction

Obtained by using high doses of chemotherapy

- Severe bone marrow hypoplasia
- Allowing re-growth of normal residual stem cells to re-grow faster than leukemic cells.

Remission: defined as < 5% blast in the bone marrow

- Normal neutrophil count
- Normal platelet count
- Normal hemoglobin level

2. Consolidation

- Different or same drugs to those used during induction
- High doses of chemotherapy
- Advantage: Delays relapse and improved survival

3. Maintenance

- Smaller doses for longer period
- Produce low neutrophil counts & platelet counts
- Objective is to eradicate progressively any remaining leukemic cells.

Acute Myeloid Leukemia	Acute Lymphoid Leukemia
☑ Induction	☑ Induction
☑ Consolidation	☑ Consolidation
☒ No maintenance	☑ Maintenance
CNS prophylaxis for selected groups only	CNS prophylaxis for all patients

Tables

Table 47-1. Normal Values for Peripheral Blood Cells

Cell Type and Size	Mean	Range
Hemoglobin	Women: 14 g/dL	Women: 12-16 g/dL
	Men: 15.5 g/dL	Men: 13.5-17.5 g/dL
Hematocrit	Women: 41%	Women: 36%-46%
	Men: 47%	Men: 41%-53%
Reticulocyte	1%	0.5%-1.5%
Count	60,000/mcL	35,000-85,000/mcL
Mean corpuscular volume	80-100	
Platelet count	250,000/mcL	150,000-400,000/mcL
Total white count	7400/mcL	4500-11,000/mcL
Neutrophils	4400/mcL (40%-60%)	1800-7700/mcL
Lymphocytes	2500/mcL (20%-40%)	1000-4800/mcL
Monocytes	300/mcL (<5%)	

Table 48-7. Laboratory Aids to Distinguish between Acute Myeloblastic Leukemia and Acute Lymphoblastic Leukemia

	Acute Myeloblastic Leukemia (AML)	Acute Lymphoblastic Leukemia (ALL)
Morphology of blasts	Granules in cytoplasm	Agranular basophilic cytoplasm
	Auer rods*	Regular, folded nucleolus
	Multiple nucleoli	
FAB subclassification	L_1-L_3	M_1-M_7
Histochemistry	Myeloperoxidase positive	Myeloperoxidase negative, PAS positive
Cytoplasmic markers	-	Tdt positive
Surface markers (% of cases)	-	B-cell markers (5%)
		T-cell markers (15%-20%): CD2, CD3, or CD5
		CALLA (50%-65%): CD10
Cytogenetic and oncogenetic	M_3: t(15;17)	L3: t(8;14)
	M_5: t(9;11)	Abnormal ALL: Ph'*bcr-abl*

*Auer rods are a linear coalescence of cytoplasmic granules that stain pink with Wright's stain.
CALLA, common acute lymphoblastic leukemia antigen; FAB, French-American-British classification system; PAS, periodic acid-Schiff stain.

Table 48-8. French-American-British (FAB) and World Health Organization (WHO) Classifications of Acute Leukemia

FAB Classification of Acute Myeloid Leukemia (AML)
M_0-Acute myelocytic leukemia with minimal differentiation
M_1-Acute myelocytic leukemia without maturation
M_2-Acute myelocytic leukemia with maturation (predominantly myeloblasts and promyelocytes)
M_3-Acute promyelocytic leukemia
M_4-Acute myelomonocytic leukemia
M_5-Acute monocytic leukemia
M_6-Erythroleukemia
M_7-Megakaryocytic leukemia
FAB Classification of Acute Lymphoblastic Leukemia (ALL)
L_1-Predominantly *small* cells (twice the size of normal lymphocyte), homogeneous population; childhood variant
L_2-Larger than L_1, more heterogenous population; adult variant
L_3-*Burkitt-like* large cells, vacuolated abundant cytoplasm

Table 48-9. Prognostic Factors in Acute Myeloid Leukemia

Clinical
Age >60 yr (median age for acute myeloid leukemia, 65 yr)
Therapy related or with antecedent hematologic disorder (e.g., myelodysplastic syndrome, myeloproliferative neoplasm, aplastic anemia)
Poor performance status
White blood cell count >20,000-30,000/mm^3
Presence of extramedullary disease sites
Biologic
Karyotype: favorable, intermediate, poor (see below)
Immunophenotype: biphenotypic
Abnormal fms-like tyrosine kinase 3 caused by mutation or internal tandem duplication
Multidrug resistance protein expression
Cytogenetic
Favorable
t(15;17)(q22;q12-21)
inv(16) or t(16;16) or del(16q)
t(8;21)(q22;q22)
Intermediate
Normal karyotype
Trisomy +8 only
t(9;11)(p22;q23)
Adverse
Complex (≥3 abnormalities)
Inv(3)(q21q26) or t(3;3)(q21;q26)
Deletion (5q- or 7q-), minus 5, minus 7
Translocations (6;9) or (9;22)
Abnormalities of 11q23 excluding t(9;11)

Table 48-10. Prognostic Factors in Acute Lymphoblastic Leukemia

Factor	Favorable	Unfavorable
Age	2-10 yr	<2 yr or >10 yr
White blood cell count at diagnosis	<30,000	>50,000
Phenotype	Precursor B	Precursor T
Chromosome number	Hyperdiploidy	Pseudo/hypodiploidy, near tetraploidy
Chromosome abnormality	t(12;21)	*c-myc* Alterations: t(8;14), t(2;8), t(8;22) mixed lineage leukemia alterations (11q23); Ph chromosome t(9;22)
Central nervous system disease at diagnosis	No	Yes
Sex	Women	Men
Ethnicity	Caucasian	African American, Hispanic
Time to remission	Short (7-14 days)	Prolonged time to remission or failure to achieve remission

What is the definition of leukemia?
o Presence of more than 5% blast cells in the blood
Symptoms of leukemia depend on the type of blood disorders that accompany it:
o RBC are affected or low production > symptoms of anemia: Pallor, palpitations, heart failure, fatigue, dyspnea.
o Platelets: Bleeding, epistaxis, mucosal bleeding
o WBC: Infection; fever, rigors, chills , sepsis, weight loss, etc
Which type of leukemia is a disease of pediatrics and is very responsive to therapy (curable)?
o Acute lymphoblastic leukemia
Why is chemotherapy more effective with ALL?
o MOA of chemotherapy: Damages the DNA
o In ALL cells replicate rapidly and have an abundance of abnormal DNA
Hypergranular promyelocytic leukemia (M3) subtype of AML:
o Most curable
o Cells contain Auer rods (initiates DIC). Causes DIC
o Chromosomal translocation at t(15,17)
M4 and M5 are the most common subtypes of AML
o L3 subtype of ALL is called: Burkitt's-cell type and is **highly curable**
Which type of leukemia is commonly associated with down's syndrome?
o AML
o Although AML affects adults more, it is common among children w/Down syndrome
o Very sensitive to chemotherapy
Which type of leukemia needs CNS prophylaxis?
o ALL (crosses BBB)
What are induction, consolidation and maintenance? And what is the most common complication of treatment of acute leukemia?
o Induction: Heavy doses of chemotherapy to kill all blast cells and cause bone marrow hypoplasia + massive blood transfusion
o Consolidation: high doses of different drugs
o Maintenance: smaller doses for longer period
o The most common complication is infection and it is usually what kills the patient – that's why you must give antibiotics
Which type of leukemia can cause symptoms of hemolysis?
o CLL
o Jaundice, decreased Hb and splenomegaly
What is the most common indication for bone marrow transplantation?
o CML
Philadelphia chromosome:
o Better prognosis
o T(9,22)
o Associated with CML
o Treated by tyrosine kinase inhibitors
What are the most common complications of bone marrow transplantation?
o GVHD (graft versus host disease)
o Second most common is infection
What is myelodysplasia (Myelodysplastic syndrome)?
o A group of acquired bone marrow disorders that are due to a defect in stem cells: bone marrow failure with abnormalities of myeloid cell lines (RBCs, granulocyte/monocytes & platelets)
o Mainly in the elderly, and presents with symptoms of anemia, infection or bleeding due to pancytopenia.
High mortality & morbidity.
o **Has the potential to transform into AML**. [Blast cells 5-20% ≠ AML] [AML → Blasts > 20%]

MCQs

1- A 30-year-old man has had a progressively worsening productive cough for one month. On physical examination, a few small non-tender lymph nodes are palpable in the axillae, and the tip of the spleen is palpable. Laboratory studies show Hgb 10.2 g/dl, Hct 31.1%, MCV 90 fL, WBC count 67,000/microliter, and platelet count 36,000/microliter. Microscopic examination of his peripheral blood smear shows many **blasts with Auer rods.**

Which of the following is the most likely diagnosis?

A - Leukemoid reaction
B - **Acute myelogenous leukemia**
C - Chronic lymphocytic leukemia
D - Acute lymphoblastic leukemia
E - Leukoerythroblastosis

2- CNS involvement is more common in:
A- Acute Lymphocytic Leukemia
B- Chronic Lymphocytic Leukemia
C- Acute Myelogenous Leukemia
D- Chronic Myelogenous Leukemia

3- The Philadelphia chromosome observed in which one of the following leukemia:
A- Chronic Myeloid Leukemia
B- Acute Lymphocytic Leukemia
C- Neither
D- Both

References

- Pathophysiology – Concepts of Altered Health States
- CECIL Essentials of Medicine
- Step-Up to Medicine
- 429's Team Work