Al Mustaqbal University College
Department of Pharmacy
4th stage
Toxicology

Lect. 8

TOXICOLOGY OF THE LEUKON

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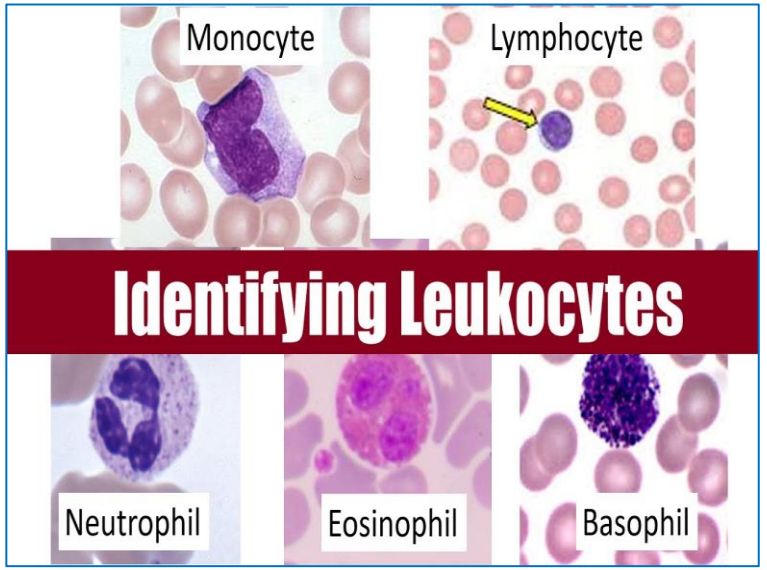
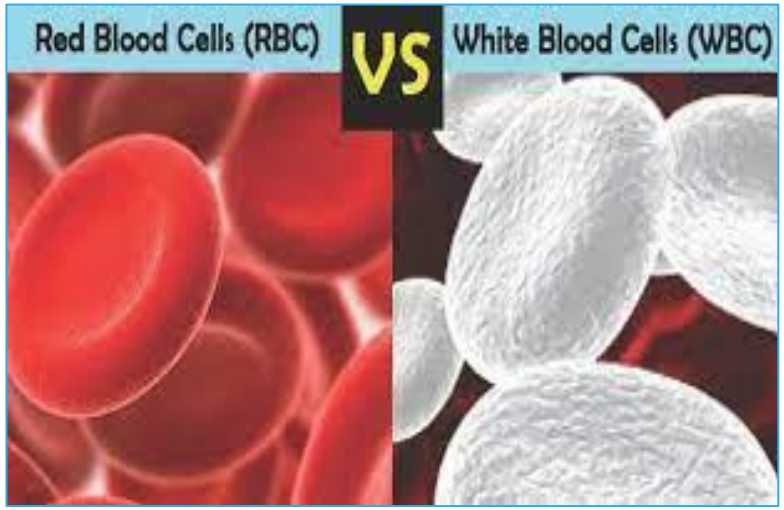
Components of Blood Leukocytes

- ✓ The leukon consists of leukocytes, or white blood cells.
- ✓ They include:
  1. Granulocytes: which may be subdivided into neutrophils, eosinophils, and basophils.
  2. Agranulocytes, may be subdivided into monocyte and lymphocyte.



WBCs VS RBCs

- ✓ WBCs are nucleated ameboid cells that are phagocytic.
- ✓ They play a central role in the inflammatory response and host defense.
- ✓ Unlike the RBCs, which reside exclusively within blood, WBCs generally pass through the blood on their way to the extravascular tissues, where they reside in large numbers.



Evaluation of Granulocytes

- ✓ The most informative test to assess the neutrophil compartment is the blood neutrophil count.
- ✓ In the blood, neutrophils are distributed between circulating and marginated pools.
- ✓ A blood neutrophil count assesses only the circulating pool, which remains between 1800/µL and 7500/µL in a healthy adult human.

Evaluation of Granulocytes

- ✓ In humans, clinically significant neutropenia occurs when the blood neutrophil count is less than 1000/µL,
- ✓ But serious recurrent infections do not usually occur until counts fall below 500/µL

Toxic Effects on Granulocytes

- ✓ Effects on Proliferation
- ✓ Effects on Kinetics
- ✓ Effects on Function

Effects on Granulocytes Proliferation

- ✓ As a hematopoietic tissue, the high rate of proliferation of neutrophils makes their progenitor and precursor susceptible to inhibitors of mitosis.
- ✓ Such effects by cytotoxic drugs are generally nonspecific, as they similarly affect cells of the dermis, gastrointestinal tract, and other rapidly dividing tissues.
- ✓ Agents that affect both neutrophils and monocytes pose a greater risk for toxic sequelae, such as infection .

Effects on Granulocytes Proliferation

- ✓ Such effects tend to be dose-related.
- ✓ It is most commonly seen with cytoreductive cancer chemotherapy drugs.
- ✓ However, this is changing, as more cancer cell–targeted

Effects on Granulocytes Proliferation

- ✓ The toxicity associated with cytotoxic drugs, remains important, with serious manifestations that include febrile neutropenia associated with life-threatening infections.

Effects on Granulocytes Proliferation

- ✓ Cytotoxic drugs vary in their mechanism, the kinetics of the cytopenias they induce, and how individual patients or animals respond.
- ✓ Most act to inhibit DNA synthesis or directly attack its integrity through the formation of DNA adducts or enzyme-mediated breaks.
- ✓ While cytoreductive drugs such as alkylating agents, cisplatin, and nitrosoureas can be toxic to both resting and actively dividing cells, nonproliferating cells such as metamyelocytes, bands, and mature neutrophils are relatively resistant.

Effects on Granulocytes Kinetics

- ✓ Chemicals that affect granulocyte kinetics can cause neutropenia or neutrophilia that has variable toxicologic significance.
- ✓ Neutrophilia is an increase in circulating neutrophils above that expected in a healthy individual of the same age, sex, race and physiological status.
- ✓ Neutropenia is a condition with lower-than-normal levels of neutrophils, it might happen due to an infection, but can result from cancer treatment.

Effects on Granulocytes Kinetics

Neutrophil disorders

Neutropenia

< 1500 /cu.mm.

- Viral infection
- Drug
- Aplastic anemia
- Cyclic neutropenia

Neutrophilia

> 7500 /cu.mm

- bacterial infection
- Inflammation
- Acute blood loss
- Acute hemolysis
- stress

Effects on Granulocytes Kinetics

- ✓ Dexamethasone has long been known to cause neutrophilia through enhanced release of mature neutrophils from the bone marrow.

Effects on Granulocytes Function

- ✓ Ethanol and glucocorticoids, may impair phagocytosis and microbe ingestion in vitro and in vivo.
- ✓ Iohexol and ioxaglate, components of radiographic contrast media, have also been reported to inhibit phagocytosis.

Effects on Granulocytes Function

- In addition to glucocorticoids, several drugs and nontherapeutic chemicals have been shown to inhibit neutrophil chemotaxis.
- Examples include macrolide antibiotics, which suppress the expression of the adhesion molecule ICAM; zinc salts, which are found in antiacne preparations; the insecticide chlordane.

Leukocytes toxicity

1. Idiosyncratic Toxic Neutropenia
2. Idiosyncratic xenobiotic-induced agranulocytosis
3. Leukemia

Idiosyncratic Toxic Neutropenia

- ✓ Such toxicity occurs in specifically conditioned individuals, and is therefore termed "idiosyncratic."
- ✓ While rare, the seriousness of this disorder, as with aplastic anemia, makes it among the most important hematotoxicities.
- ✓ Mechanisms of idiosyncratic damage often do not relate to pharmacologic properties of the parent drug, which makes managing this risk a particular challenge.

Idiosyncratic Toxic Neutropenia

- ✓ Chemicals that unexpectedly damage neutrophils and granulocyte precursors.
- ✓ Particularly those inducing agranulocytosis, which is characterized by a profound depletion in blood neutrophils to less than 500/µL.
- ✓ The severity of the neutropenia often causes severe sepsis or localized infections, such as sore throat, pneumonia, or various cutaneous infections.

Idiosyncratic xenobiotic-induced agranulocytosis

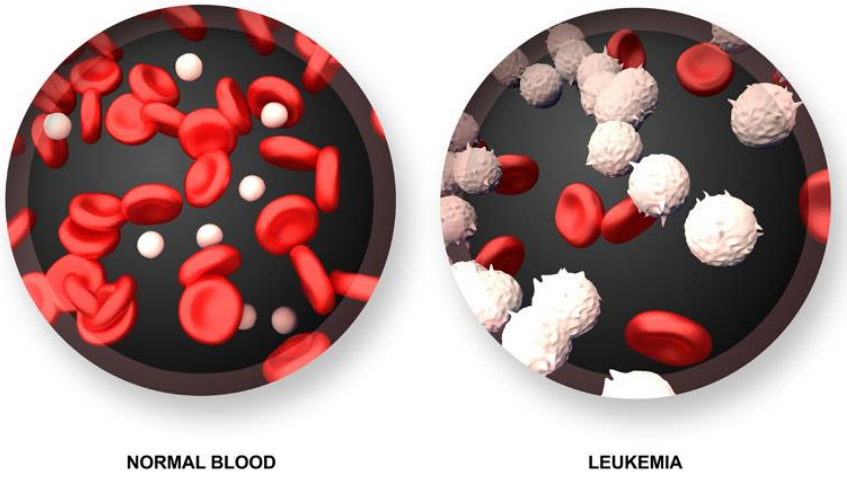
- ✓ This toxic response involves a sudden depletion of circulating neutrophils concomitant with exposure.
- ✓ It may persist as long as the chemical or its metabolites persist in the circulation.
- ✓ Hematopoietic function is usually restored when the chemical is detoxified or excreted.
- ✓ Suppression of granulopoiesis, however, is more prevalent than peripheral lysis of neutrophils and is asymptomatic unless sepsis occurs.

Idiosyncratic xenobiotic-induced agranulocytosis

- ✓ The incidence of drug-induced idiosyncratic agranulocytosis ranges from 2 to 15 cases per million patients exposed to drugs per year.
- ✓ While all drugs may be causative, the most commonly incriminated drugs include antithyroid agents and antibiotics, particularly sulfonamides.
- ✓ Clozapine-induced agranulocytosis (CIAG) is unique, as a genetic predisposition has been established.

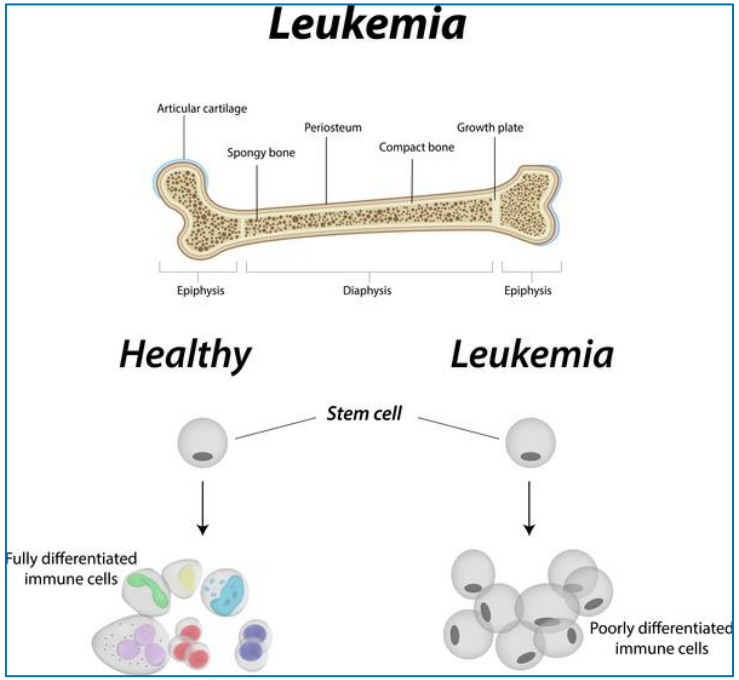
Leukemia

- ✓ Leukemia is a type of blood cancer that develops in the bone marrow , where blood cells are made.
- ✓ The cancer causes the body to make a large amount of abnormal white blood cells, which normally protect the body against infection.
- ✓ All of those damaged white blood cells crowd out healthy blood cells



Leukemia

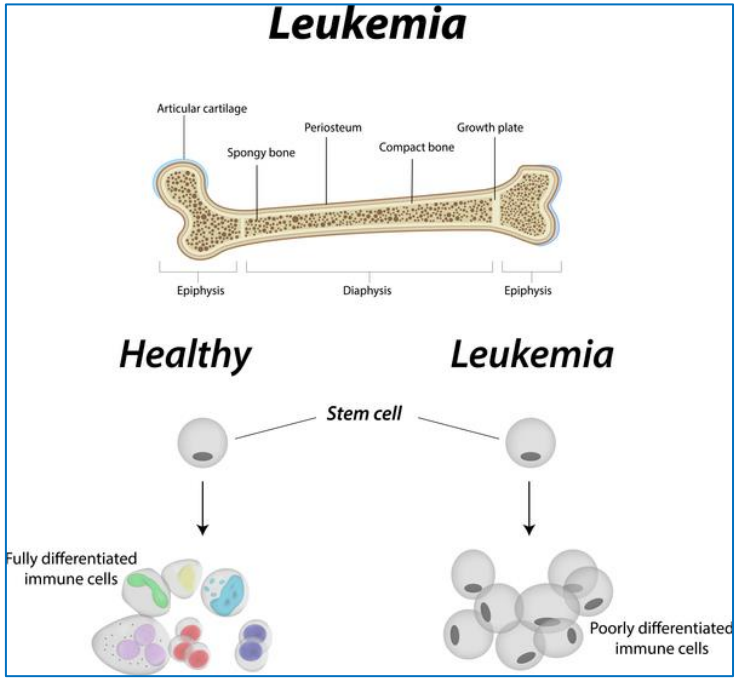
- ✓ Leukemia is the sixth leading cause of cancer deaths among males and females in the United States (2013).
- ✓ Leukemias arise when hematopoietic stem or progenitor cells (HSC/HPC) in the bone marrow undergo:
  1. Either uncontrolled proliferation
  2. Or clonal expansion and cannot differentiate normally into mature blood cells.



Leukemia

- ✓ Leukemias are broadly characterized as myeloid or lymphoid depending on the lineage of origin.
- ✓ Based on the stage of differentiation and rate of clonal expansion, they are also characterized as:

1. Either acute (rapid onset, immature blast cells)
2. Or chronic (more gradual onset over months or years, more mature cells).



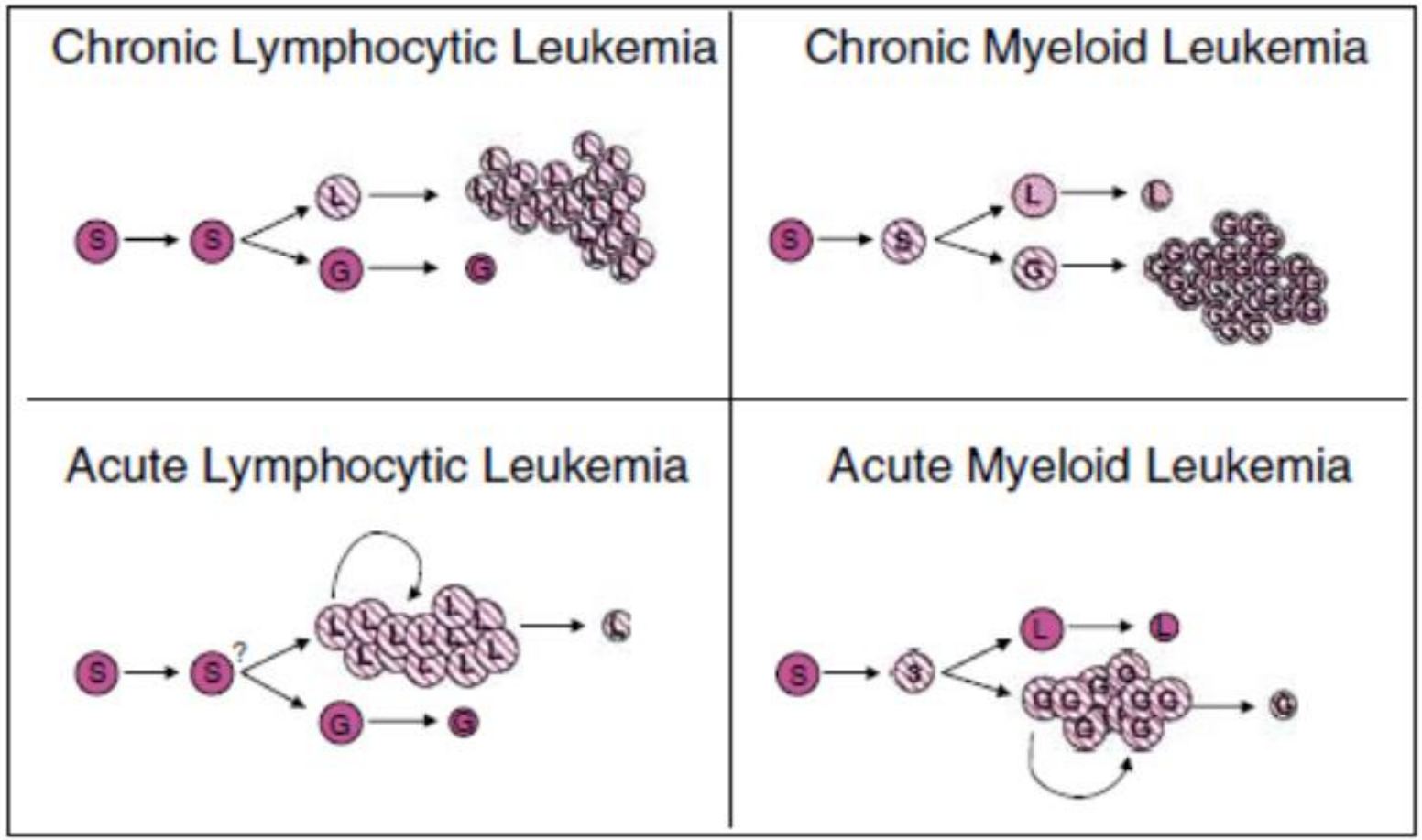
Types of leukemia

1. Lymphocytic leukemia (also known as lymphoid or lymphoblastic leukemia) develops in the white blood cells called lymphocytes in the bone marrow.
2. Myeloid (also known as myelogenous) leukemia may also start in white blood cells other than lymphocytes, as well as red blood cells and platelets.

Types of leukemia

1. Acute lymphoblastic leukemia (ALL),
2. Acute myeloid leukemia (AML) also known as acute nonlymphocytic leukemia (ANLL),
3. Chronic lymphoblastic leukemia (CLL),
4. Chronic myeloid leukemia (CML).

✓ Within these categories numerous subtypes exist and are classified according to morphologic, cytogenetic, immunophenotypic, and, molecular characteristics,



Development of myeloid and lymphoid leukemias within the context of hematopoietic cell hierarchy. Hematopoietic stem cells (HSCs; S) produce granulocytic (G) and lymphocytic (L) precursors, which then go on to generate smaller differentiated cells. Genetic and/or epigenetic aberrancies (striped) in stem or progenitor cells lead to a neoplastic accumulation of cells due to hyperproliferation and decreased apoptosis.

General Mechanisms of Leukemogenesis

Leukemogenesis is a multistep process involving the acquisition of various combinations of

1. **Chromosomal aberrations**
2. **Genetic mutations**
3. **Epigenetic modifications**

That transform a normal stem cell into a leukemic stem cell (LSC)

General Mechanisms of Leukemogenesis

The resulting altered gene expression patterns disrupt critical hematopoietic processes such as signal transduction, alternative splicing, and epigenetics.

Also give rise to cellular phenotypes such as increased proliferation or survival, block of differentiation, and immortalization.

THANK YOU