***Lecture 4****.* ***Pharmacology of drugs affecting***

***the blood system***

1. ***Pharmacology of drugs affecting erythropoiesis, leukopoiesis,***

***various types of anemia and hemoglobinopathies***

 Hematopoiesis is blood cell production. Body continually makes new blood cells to replace old ones. Hematopoiesis ensures to have a healthy supply of blood cells to supply oxygen to the tissue (red blood cells), fight infection (white blood cells) and clot blood when are injured (platelets). Most blood cells get made in the bone marrow. Red blood cells, or erythrocytes, carry oxygen from lungs to organs. The production of red blood cells is called erythropoiesis.White blood cells, or leukocytes, fight infection and protect from harmful invaders, or germs. They also destroy abnormal cells. The production of white blood cells is called leukopoiesis. Broadly, the types of white blood cells are: Neutrophils. Basophils. Eosinophils. Monocytes. Lymphocytes

 Neutrophils, basophils and eosinophils have similar functions and can be grouped together and called granulocytes. The other types of white blood cells are monocytes and lymphocytes.

*Drugs affecting the blood system are divided into two groups:*

1) drugs that regulate *erythropoiesis* (stimulators and inhibitors);

2) drugs that regulate *leukopoiesis* (stimulators and inhibitors)

*Leukopoiesis stimulators.* A decrease in the number of leukocytes occurs with toxic effects on the bone marrow of toxic and medicinal substances (benzene, arsenic, antitumor agents, etc.), ionizing radiation, microbial toxins, etc. A decrease in the number of white blood cells is a life threat.Leukopoiesis stimulators increase the number of leukocytes.

*Еrythropoiesis stimulators*enhance hemoglobin synthesis and production of red blood cells, increasing their content in the blood.

*Inhibitors*are the opposite.

 *Erythropoiesis* is regulated by a glycoprotein hormone – *erythropoietin.**Erythropoietin* is produced mainly in the kidneys. This hormone causes an increase in the production of red blood cells.

 Erythropoiesis is stimulatedby a decrease in oxygen delivery to tissues, which is detected by the kidneys. The kidneys, in response to tissue hypoxia, secrete the hormone *erythropoietin,*which stimulates erythropoiesis.

 Anemia signs and symptoms vary depending on the cause and severity of anemia. Depending on the causes of anemia. Signs and symptoms: Fatigue, Weakness, Pale or yellowish skin, Irregular heartbeats, Shortness of breath, Dizziness, Chest pain, Cold hands and feet, Headaches.

 Anemia is defined as a below-normal plasma hemoglobin
concentration resulting from a decreased number of circulating red
blood cells or an abnormally low total hemoglobin content per unit of
blood volume. General signs and symptoms of anemia include fatigue, rapid heartbeat, shortness of breath, pale skin, dizziness, and insomnia.

Anemia can be caused by chronic blood loss, bone marrow
abnormalities, increased hemolysis, infections, malignancy,
endocrine deficiencies, renal failure, and a number of other disease
states. A large number of drugs cause toxic effects on blood cells,
hemoglobin production, or erythropoietic organs, which, may cause
anemia.
 Nutritional anemias are caused by dietary deficiencies of substances
such as iron, folic acid, and vitamin B12 (cyanocobalamin) that are
necessary for normal erythropoiesis. Individuals with anemia that has a genetic basis, such as sickle cell disease, can benefit from pharmacologic treatment with actions beyond nutritional supplementation, such as *hydroxyurea*.

 Anemia can be at least temporarily corrected by transfusion of whole
blood. Iron is stored in the intestinal mucosal cells, liver, spleen, and bone marrow as *ferritin* (an iron–protein complex) until needed by the body.
Iron is delivered to the marrow for hemoglobin production
by a transport protein, namely *transferrin.* Iron deficiency results from *acute or chronic blood loss*, from *insufficient intake* during periods of accelerated growth in
children, and in heavily menstruating or pregnant women. Iron deficiency results

from a negative iron balance due to depletion of iron stores and/or inadequate intake,
culminating in hypochromic microcytic anemia (*due to low
iron and small-sized red blood cells*).

 Supplementation with elemental iron corrects the iron deficiency.
The Centers for Disease Control and Prevention (CDC) recommends
150 to 180 mg/day of oral elemental iron administered in divided
doses two to three times daily for patients with iron deficiency
anemia.

*Pharmacokinetics:*Iron is absorbed after oral administration.

Acidic conditions in the stomach keep iron in the reduced ferrous
form, which is the more soluble form. Iron is then absorbed in the
duodenum. [Note: The amount absorbed depends on the current
body stores of iron. If iron stores are adequate, less will be absorbed.
If stores are low, more iron will be absorbed.]
The relative percentage of iron absorbed ↓decreases with
↑increasing doses. For this reason, *(recommended that most people take the prescribed daily iron supplement in two or three divided doses)*.

Some extended release formulations may be dosed once daily.
• ***Oral*** preparations include *ferrous sulfate*, *ferrous fumarate*, *ferrous
gluconate*, *polysaccharide iron complex*, and *carbonyl iron* formulations. Of
these preparations, *ferrous sulfate* is the most commonly used form of iron
due to its high content of elemental iron and relatively low cost.
**• *Parenteral*** formulations of iron, such as *iron dextran*, *sodium ferric
gluconate complex*, and *iron sucrose*, are also available. Macrophages phagocytize *iron dextran* and release iron from the dextran molecule. With *iron sucrose*, specific exchange mechanisms transfer iron to transferrin. *Parenteral administration treats iron deficiency rapidly, oral administration may take several week*.

Hemoglobin (Hb) represents the major part of iron in the body:
- Hb is essential oxygen transporter to tissues from the lung.
- Iron is also present in other proteins (myoglobin
and cytochromes).
- 70% of iron is Hb, 10-20% in ferritin and hemosidrin, 10% in myoglobin, < 1% in cytochromes and in other iron-containing enzymes e.g. transferrin.
- Women loose iron more than men (menstruation and pregnancy).

Food containing iron as heme or complexed with other organic compounds.
- Iron therapy is used as iron salts or iron complexed with inorganic substances
*Absorption:*- Mainly from upper GIT.
- Normally 5-10% of dietary iron is absorbed (=0.5-1 mg daily)
- In iron deficiency anaemia and in increased requirement, iron absorption is increased (1-2 mg/day in menstruating women and 3-4
mg/day in pregnant women).

Infants and adolescents require more iron.
- Iron in Hb and myoglobin (red meat) may be absorbed as hemin (the ferric form of heme) without first having to be broken down into elemental iron.
- Iron complexed with dietary plants is less absorbed.
- Non-heme iron and iron in inorganic iron salts and complexes must be converted to ferrous form before absorption.
- *HCl* and *vitamin C* enhance iron absorption whereas chelators and complexing agents suppress iron absorption.
- Iron as ferrous is transported actively across the intestinal mucosa converted to ferric iron within the mucosal cells.
- The absorbed ferric iron is transported from the mucosal cells to plasma via trans-ferrin or converted to ferritin and stored in the mucosal cells (depending on the total body iron stores and iron requirements).
*Distribution:*- The plasma form of iron is transferrin.
- Iron is transported to the developing erythroid cells in bone marrow (BM).
- Transferrin receptors in BM bind the transferrin-iron complex and releasing it
within the erythroid cell.
*Storage*:
- Iron is stored in two forms: ferritin & hemosiderin.
- Ferritin is a core crystal of ferric hydroxide covered by a protein shell of
apoferritin.
- Hemosiderin is aggregates of ferric core crystals with or without apoferritin.
- Storage sites includes: macrophages in the liver, spleen, BM. Ferritin is also present in intestinal mucosa and plasma.
- Plasma or serum ferritin level is the expression of total body iron stores.
*Elimination:*- No specific mechanism of elimination.
- Loss of iron (1 mg/day) is through exfoliation of intestinal mucosal cells,
bile, urine and sweat.
- Intestinal absorption of iron regulates iron balance in the body.
- The balance of the amount of ferritin present and rate of erythropoiesis is
important.
- Increased number of transferrin receptors ⭡erythropoiesis ⭡rate of iron
absorption.
- In iron deficiency transferrin is increased and ferritin is increased which leads to
inhibition of further iron absorption.

 *Regulation of iron pharmacokinetics:* *Indication of iron therapy:*In iron deficiency anemia states: premature babies, children, pregnant, lactating women, post gastrectomy and malabsorption.

 **Classification of drugs:**



**Pharmachologic effect of IRON ‘s drug**

 When iron preparations are taken orally, Fe3+ ions from the intestines enter the bloodstream only through active absorption, which explains the **impossibility of overdose (and intoxication).**

 The degree of absorption **Fe3+** after oral administration depends on the degree of iron deficiency (**the greater the deficiency, the higher the absorption**) and on the dose of the drug (**the higher the dose, the worse the absorption**).

 Absorbed mainly in the duodenum and small intestine.

 The non-absorbed part is excreted in the feces, mixing with hydrogen sulfide and staining the feces black.

 Doses and duration of treatment depend on the degree of iron deficiency.

 After normalization of the hemoglobin concentration, have to continue taking the drug for several more weeks to replenish iron stores in the body.

**Parenteral** administration treats iron deficiency rapidly, **oral** administration may take several weeks.

***Side effect***

Allergic reactions: skin manifestations.

From the digestive system: rarely - constipation, diarrhea, abdominal pain, nausea, vomiting. When taking iron-containing drugs, it is possible to stain the feces in a dark (black) color, which has no clinical significance.

***Contraindications for use***

Hypersensitivity to the components of the drug;

iron absorption disorders;

anemia not associated with iron deficiency.

After **İM** administration, it enters the bloodstream through the lymphatic system. Time to reach Cmax - 24 hours.

  **İM** administration: in rare cases - arthralgia, swollen lymph nodes, fever, headache, dyspepsia (nausea, vomiting); rarely - allergic reactions.

Local reactions: skin staining, inflammation.

**İM, İV** administration is contraindicated in the first trimester of **pregnancy.**

***Drug interaction***

 With the simultaneous use of iron salts, the absorption of drugs such as **tetracyclines, ciprofloxacin, levofloxacin, ofloxacin, penicillamine, levodopa, carbidopa and methyldopa** is reduced.

 In patients receiving replacement therapy with **levothyroxine sodium**, iron salts reduce its absorption.

 Iron absorption is reduced when **cholestyramine, antacids** (containing aluminium, magnesium, calcium, bismuth) and **calcium and magnesium** supplements are taken concomitantly.

 The simultaneous use of iron salts and NSAIDs can enhance the damaging effect of iron on the gastrointestinal mucosa.

 **All of the above funds are recommended to be taken 3-4 hours before or after administration.**

 **Ascorbic acid and citric acid** increase iron absorption.

**Ethanol** increases iron absorption and the risk of toxic complications.

 Gastrointestinal (GI) disturbances caused by local irritation (abdominal pain, constipation, nausea, diarrhea) and dark stools are the most common adverse effects of **oral iron supplements**.

 **Parenteral** iron formulations may be used in those who cannot tolerate or inadequately absorb oral iron, as well as those receiving *erythropoietin* with hemodialysis or chemotherapy. Fatal hypersensitivity and anaphylactoid reactions can occur in patients receiving parenteral iron (mainly *iron dextran* formulations). A test dose should be administered prior to *iron dextran.*

**In addition,** intravenous iron should be used cautiously in the presence of active infections. [Note: Iron is essential for bacterial growth.]

The specific antidote is **Deferoxamine.**

 ***Pharmachologic effect of Deferoxamine -*** complexing compound.

Forms complexes mainly with trivalent iron and aluminum ions; binds divalent ions to a lesser extent.

 Deferoxamine can bind iron, which is in free form or is part of ferritin and hemosiderin, as well as bind aluminum in tissues. The resulting compounds are excreted in the urine, which leads to a decrease in pathological deposits of iron and aluminum in the tissues.

 Deferoxamine is poorly absorbed from the gastrointestinal tract. After parenteral administration, deferoxamine forms complex compounds (chelates) with metal ions, which are then excreted with the urine. ***Indications***

 Hemosiderosis (especially with thalassemia and other chronic anemias).

 Acute iron poisoning.

Deferoxamine can stain urine reddish brown.

**İM, İV** (infusion)

 **Macrocytic anemias** are most often the result of **vitamin B12 and folic acid** deficiency. Macrocytosis is observed in various clinical conditions. Macrocytosis associated with excess RBC membrane occurs in patients with chronic liver disease, may occur in patients with chronic alcohol use in the absence of folic acid deficiency.

**Folic acid (folate)**

 Both vitamin **В12 and folate deficiency** can cause similar symptoms.

 **Folic acid** is rapidly absorbed in the jejunum unless abnormal pathology is present. Oral folic acid administration is nontoxic and at high doses, excess vitamin is excreted in the urine.

 Normally, human serum contains 6-20 ng / ml of folate.

***NB!*** Taking folic acid during pregnancy reduces the risk of neural tube defects in the fetus. During pregnancy, it protects against the action of teratogenic factors. Contributes to the normal development and functioning of the placenta.

 **Folic acid** stimulates erythropoiesis, participates in the synthesis of amino acids (including methionine, serine), nucleic acids, purines and pyrimidines, in the metabolism of choline, histidine.

**Pharmacokinetics.** After admission, it is well absorbed from the gastrointestinal tract. Plasma protein binding is high. Metabolized in the liver and tissues. Excreted with bile and urine. Penetrates through the BBB, placenta, into breast milk.

 The method and mode of **application of dosing** drugs depends on its form of produce and other factors. The optimal dosing regimen is determined by the doctor. Compliance of the dosage form of a particular drug with indications for use and dosing regimen should be strictly observed.

***Drug interaction***

 With **chloramphenicol, neomycin, polymyxins, tetracyclines,** the absorption of folic acid decreases.

 With the simultaneous use of folic acid, plasma concentrations of **anticonvulsant drugs** (phenobarbital, phenytoin, primidone), **estrogens, contraceptives** may decrease.

 With **antacids** (including calcium, aluminum and magnesium preparations), **cholestyramine, sulfonamides** (including sulfasalazine), the absorption of folic acid is reduced.

**Methotrexate, pyrimethamine, triamterene, trimethoprim** inhibit dihydrofolate reductase and reduce the effect of folic acid.

***Cyanocobalamin (vitamin 812)***

 Deficiencies of **vitamin B12** can result from low dietary levels, poor absorption, or a loss of activity of the receptor needed for intestinal uptake of the vitamin.

 In addition to general signs and symptoms of anemia, **vitamin B12** deficiency anemia may cause tingling (pins and needles) in the hands and feet, difficulty walking, dementia, and, in extreme cases, hallucinations, paranoia, or schizophrenia.

 ***NB!*** Folic acid administration alone reverses the hematologic abnormality and, thus, masks the **vitamin B12 deficiency**, which can then proceed to severe neurologic dysfunction and disease. Therefore, megaloblastic anemia should by **combination of folic acid and vitamin B12.**

**Erythropoietin and darbepoetin**

 Peritubular cells in the kidneys respond to hypoxia and synthesize and release **erythropoietin, (EPO)**, a glycoprotein. EPO stimulates stem cells to differentiate into proerythroblasts and promotes initiation of hemoglobin formation. Thus, **EPO** regulates red blood cell proliferation and differentiation in bone marrow. A long-acting form of erythropoietin – **darbepoetin**.

 These agents are well tolerated and are administered intravenously in renal dialysis patients or subcutaneously for other indications.

 Side effects such as blood pressure elevation and arthralgia may occur in some cases.

***Pharmachologic effect***

 Recombinant human **erythropoietin** is a **purified glycoprotein**.

 **Stimulates erythropoiesis.**

The synthesis of endogenous erythropoietin is carried out in the kidneys and depends on the level of blood oxygenation.

Human erythropoietin, produced by recombinant DNA technology, is effective in the treatment of anemia caused by renal disease, human immunodeficiency virus infection, bone marrow disorders, prematurity, and malignancy.

İf the hemoglobin level exceeds 10 g/dl, doses of *epoetin* or *darbepoetin* should be reduced or treatment should be discontinued.

 Neither agent has any value in the acute treatment of anemia due to their delayed onset of action.

***Pharmacokinetics***

 **After the s/c injection**, the concentration of the active substance in plasma increases slowly, reaching the maximum level after 12-18 hours.

 **After multiple IV** introduction of T1/2 in adults healthy patients is 4 hours, in patients with renal failure – approx. is 6 hours; In children – approx. is 6 hours.

***Indications of Epoetin Alpha***

 The treatment of anemia associated with chronic renal failure in adults and children on hemo- or peritoneal dialysis.

 Prevention and treatment of anemia in cancer patients (receiving or not receiving chemotherapy).

 Treatment of anemia in HIV-infected patients receiving zidovudine therapy (at the level of endogenous erythropoetin ≤ 500 IU/ml).

 During of the pre-deposit program before an extensive surgery in patients with a low level of hematocrit.

 **USAGE: SC; IV**

***Special instructions***

  **Epoetin** alfa should be used with caution in patients with epilepsy and a history of seizures. Use with caution in gout.

 Prior to use, it should be ensured that patients with arterial hypertension have received effective antihypertensive therapy. If BP does not decrease despite adequate therapy, epoetin alfa should be discontinued.

 The therapeutic efficacy of epoetin alfa may decrease with iron deficiency, folic acid deficiency, vitamin B12 deficiency, aluminum intoxication, intercurrent diseases, occult bleeding, hemolysis, bone marrow fibrosis.

***Drug interaction***

 The action of epoetin alfa may be enhanced by the administration of blood products.

 The use of drugs that suppress erythropoiesis may lead to a decrease in the effectiveness of epoetin alfa.

 Epoetin alfa not be mixed with solutions of other medicinal products.

***AGENTS USED TO TREAT NEUTROPENIA***

 **Neutropenia** is a condition in which the number of neutrophils (a type of white blood cell) in the blood is reduced. The level of neutrophils is considered low if it is below 500 cells/mm3. Neutropenia often occurs after certain cancer treatments.

 **Causes of neutropenia:**

chemotherapy and radiation treatment; bone marrow diseases; lack of vitamin B12 or folic acid; congenital disorders of the bone marrow.

***Granulocyte colony-stimulating factors (G-CSF),*** such as **filgrastim** and ***granulocyte-macrophage colony-stimulating factors (GM-CSF***), such as **sargramostim**, stimulate granulocyte production in the marrow to increase neutrophil counts and reduce the duration of severe neutropenia. These agents are typically used prophylactically to reduce the risk of neutropenia following chemotherapy and bone marrow transplantation. **Filgrastim and sargramostim** can be dosed either subcutaneously or intravenously. The main difference between the available agents is in the frequency of dosing. Filgrastim and sargramostim are dosed once a day beginning 24 to 72 hours after chemotherapy.

 There is no evidence to show superiority of one agent over another in terms of efficacy, safety, or tolerability. Bone pain is a common adverse effect with these agents.

***Dosing regimen:***

 Individual, depending on the indications and treatment regimen.

***Side effect:***

 pain in the muscles or bones, dysuria, arterial hypotension, allergic-type reactions, reversible increase in the levels of LDH, uric acid in the blood plasma are possible.

**Usage: SC/ İV**

***AGENTS USED TO TREAT SICKLE CELL DISEASE***

***Disease symptoms:***

 Chest pain and difficulty breathing; joint pain, arthritis; blockage of blood flow in the spleen or liver; Severe Infections.

**Hydroxyurea**  is an oral ribonucleotide reductase inhibitor that can reduce the frequency of painful sickle cell crises in sickle cell disease, **hydroxyurea** increases hemoglobin levels, thus diluting the abnormal hemoglobin. A clinical response may take three to six months. Important side effects of **hydroxyurea** include bone marrow suppression and cutaneous vasculitis. It is important that **hydroxyurea** is administered under the supervision of a provider experienced in the treatment of sickle cell disease. **Hydroxyurea** is also used to treat acute myelogenous leukemia, psoriasis, and polycythemia.

***Pharmachologic effect***

 Hydroxyurea is a phase-specific cytostatic drug that acts in the S phase of the cell cycle.

 It blocks the growth of cells in the G1-S interphase, which is essential for radiation therapy, since there is a synergistic sensitivity of tumor cells in the G1 phase to radiation.

 By enhancing the action of the RNA reductase inhibitor - ribonucleoside diphosphate reductase, it causes suppression of DNA synthesis.

 The drug does not affect the synthesis of RNA and protein.

**Pharmacokinetics**

 After oral administration, it is quickly absorbed from the gastrointestinal tract. **CMAX drug** in blood plasma is reached 1-4 hours after taking. Eating does not affect the absorption of the drug.

 It is quickly distributed through the tissues of the body, **penetrates through the BBB.**

 T1/2 - 3-4 hours. Partially metabolized in the liver and kidneys. Is excreted **in the urine** within 12 hours and in small amounts **in the form of urea**. The drug is also excreted through the **respiratory tract** in the form of a **carbon of dioxide**. After 24 hours, in the plasma is not determined.

***Side effect:***

 On the part of the **hematopoietic organs:** leukopenia, anemia, thrombocytopenia. On the part of the **digestive system**: stomatitis, bleeding gums, anorexia, nausea, vomiting, diarrhea or constipation. On the part of the **skin:** rashes, erythema, dermatomyositis, hyperpigmentation, atrophy of the nails.

 As well as headache, dizziness, fatigue, drowsiness, increase in the content of uric acid in the blood plasma, urinary retention, fertility disorders (azoospermia, cessation of menstruation).

***Special instructions***

 Treatment with the drug should be carried out under the supervision of a physician. Before, and periodically but during treatment with the drug, it is necessary to check the functions of the bone marrow, kidneys and liver. Determination of hemoglobin, leukocytes and platelets should be carried out at least once a week throughout the entire period of drug treatment.

 During treatment with the drug may develop myelosuppression, leukopenia.

 The use of hydroxyurea can provoke generalization of infections.

During treatment, patients should drink enough fluids.

***Overdose***

 When using the drug in doses, patients develop signs of acute toxicity: soreness, swelling, followed by peeling of the palms of the hands and feet, intense generalized hyperpigmentation of the skin, and other side effects may also increase.

The specific antidote is unknown. Treatment is symptomatic.