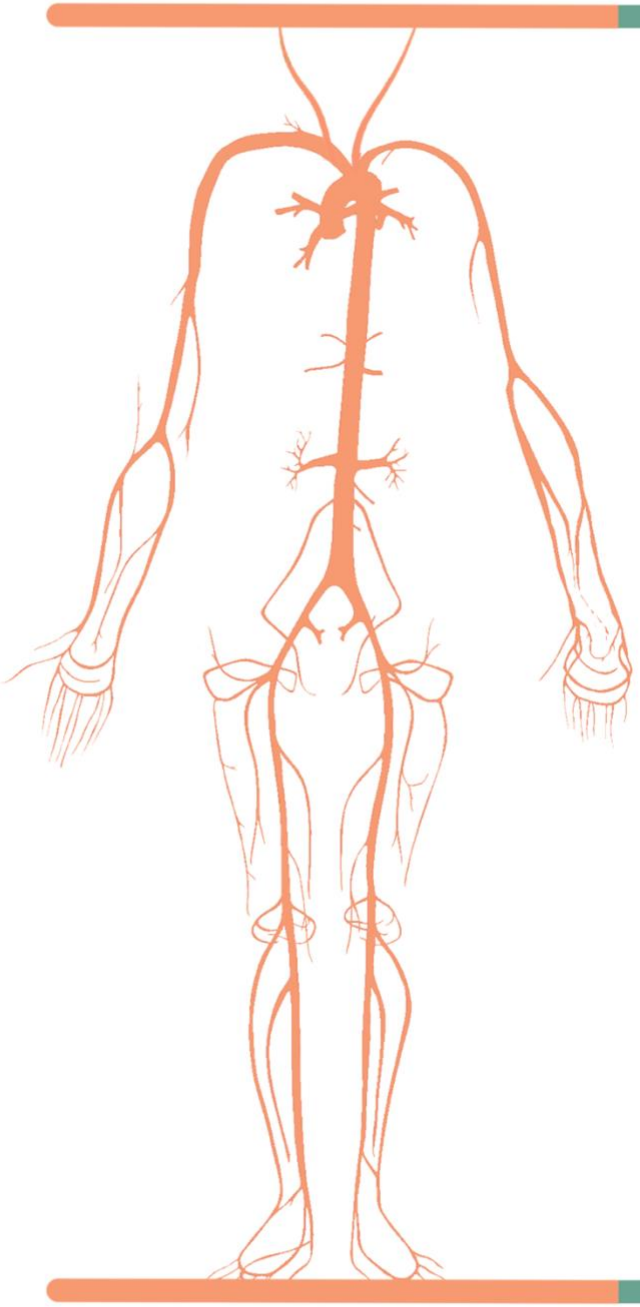
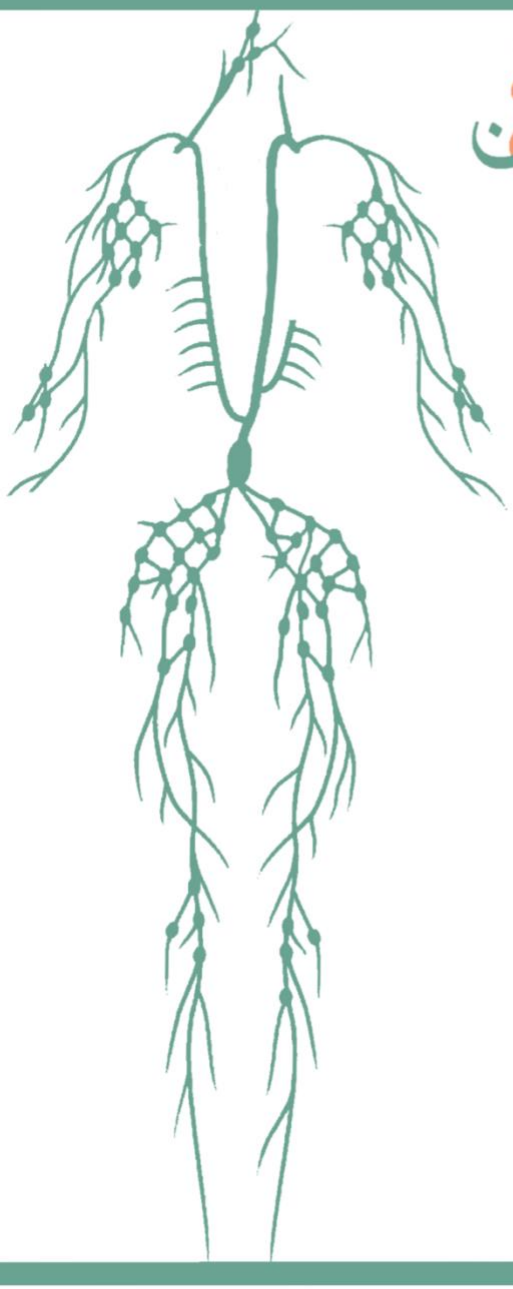
Pharmacology

HematoLymphatic





Title: Hematopoietic Growth Factors

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Hematopoietic Growth Factors

In the beginning, we discussed in the first lecture the agents used in anemias like iron, vitamin B12 and folic acid.

In this lecture we will talk about hematopoietic growth factors, so let's start.

Note: Drug doses are not for memorizing.

Hematopoietic Growth Factors:-

glycoprotein hormones that are mainly used regulate the **proliferation** and **differentiation** of hematopoietic **progenitor** cells in the bone marrow.

- They are useful in **hematologic** as well as **non-hematologic** conditions.
- They are used as potential anticancer and anti-inflammatory drugs.

Hematopoietic Growth Factors are :-

- ✓ Erythropoietin (*Epoetin alfa*)
- ✓ Colony Stimulating Factors (*CSFs*)
- ✓ Granulocyte colony – stimulating factor (*G-CSF*)
- ✓ Granulocyte – macrophage colony – stimulating factor (*GM-CSF*)
- ✓ Interleukin – 11 (*IL – 11*)
- ✓ Thrombopoietin

1) Erythropoietin:-

- ✓ **34-39 kDa glycoprotein.**
- ✓ **Was the first human hematopoietic growth factor to be isolated (in 1977).**
- ✓ This hormone was originally purified from urine of patients with **severe anemia (of course, it's not a practical way to obtain the hormone).**
- ✓ It is produced in the **kidney** in response to hypoxia through increased the rate of transcription of the gene.
- ✓ It needs active (healthy and functional) bone marrow with no nutritional deficiencies (e.g. iron deficiency), primary bone marrow disorders and suppression by drugs or chronic diseases.
- ✓ It stimulates **erythroid** proliferation and differentiation by interacting with specific receptors (JAK/STAT cytokine receptors) on red cell progenitors. Also, it facilitates the release of reticulocytes from the bone marrow.

- **Serum levels :-**
  -**Normal** serum level 20 IU/L.
  - It's **elevated** in most anemias (up to thousands)
  - **It's lowered** in anemia of chronic renal failure.

- ✓ Recombinant human erythropoietin (*rHuEPO*, or *Epoetin alfa*) is **produced in a mammalian cell expression system** (i.e. cell culture).
- ✓ After IV administration, the half-life is approximately 4-13 hours (relatively short half-life). Extra: It has a longer half-life in CRF pts.
- ✓ It is **not** cleared by dialysis.
- ✓ ***Darbepoetin alfa*** (modified form of erythropoietin) has **longer** half-life than *epoetin alfa* (given twice/week).

Indications of erythropoietin :-

Erythropoietin's indications	Dose (not for memorizing)	Notes
1- Anemia of chronic renal failure (Deficiency of erythropoietin)	**Usually small doses are sufficient; (50-150 IU/Kg) IV or SC (subcutaneously) 3 times a week.**	✓ **These patients are most likely to benefit from the treatment.** ✓ **Failure to respond is usually due to iron or folic acid deficiency.**
2- Primary bone marrow disorders and secondary anemias (e.g. aplastic anemia, myeloproliferative and myelodysplastic disorders, multiple myeloma, and bone marrow malignancies. Also, anemia of chronic inflammation, AIDS, and cancer).	**In contrast to CRF patients, these patients require higher doses (100-500 IU/Kg).**	✓ **Response is generally incomplete (because the problem is not a deficiency in erythropoietin, while in anemia of CRF the problem is a deficiency in erythropoietin).**
3- Anemia of *zidovudine* treatment.		***Zidovudine is an* anti-viral agent.**
4- Anemia of prematurity		**prematurity : under-developed bone marrow**

5- **Iron overload**		**iron toxicity, which occurs after accident IV administration of iron usually accidentally).**
6- Un**ethically, used by athletes**		**(in order to build their muscles and perform well, they seek to increase the oxygen carrying capacity of their cells by increasing the hemoglobin levels and red cells counts).**

Toxicity of erythropoietin:

- ✓ Due to rapid increase in hematocrit and hemoglobin, that will develop **hypertension and thrombotic complications (most common adverse effect).**
- ✓ Allergic reactions are infrequent and mild (since it's produced by recombinant technology).

2) Myeloid Growth Factors:-

- ✓ Originally purified from cultured human white blood cells (it's not a practical way to get these factors, since the life span of WBCs is short, and the quantities that can be obtained are very minimal).

✓ *rHuG-CSF "Filgrastim"-:*

✓ was produced in 1991.
It's produced in a bacterial cell expression system.
It's composed of 175 amino acids (not glycosylated).
Molecular weight: 18 kDa
Half-life: 2-7 hours.

✓ *Pegfilgrastim (aka. filgrastim)-:*

✓ it's covalently conjugated with polyethylene glycol (this attachment increases the duration of action).
It has much longer half-life than *rHuG-CSF*.
It can be injected once per chemotherapy cycle.

✓ *rHuGM-CSF "Sargramostim"-:*

✓ **it's produced in a yeast cell expression system**.
It's composed of 127 amino acids.
Molecular weight: 15-19 kDa.
Half-life: 2-7 hours.

A) G-CSF:-

- ✓ Works on JAK/STAT receptors on WBC progenitors.
- ✓ Stimulates **proliferation** and differentiation of progenitors committed to the neutrophil lineage.
- ✓ Activates the phagocytic **activity** of mature neutrophils and prolongs their survival in the circulation.
- ✓ Mobilizes **hematopoietic** stem cells into the peripheral circulation, this biologic effect underlies a major advance in transplantation; the use of peripheral blood stem cells (PBSCs) rather than bone marrow stem cells for autologous and allogeneic hematopoietic stem cell transplantation.

B) GM-CSF:-

- ✓ Has broader actions than G-CSF, also works on (JAK/STAT receptors).
- ✓ Stimulates proliferation and differentiation of early and late granulocytic progenitor cells as well as erythroid and megakaryocyte progenitors.
- ✓ Acts together with interleukin-2 to stimulate T-cell proliferation.
- ✓ Locally, it is an active factor of inflammation.
- ✓ Mobilizes peripheral blood stem cells , but less than G-CSF .

Clinical applications of myeloid growth factors:

In Cancer chemotherapy – induced neutropenia:

- ✓ Neutropenia is a common adverse effect of the cytotoxic drugs used to treat cancer and increases the risk of serious infection in patients receiving chemotherapy.
- ✓ Transfusion of neutropenic patients with granulocytes collected from donors is performed rarely and with limited success (cells have very short life span), so granulocyte transfusion is not practical and the discovery of these myeloid growth factors is a necessity.
- ✓ G-CSF **accelerates** neutrophil recovery after cancer chemotherapy, leading to reduced episodes of febrile neutropenia, need for antibiotics, and days of hospitalization. However, it **doesn't improve survival.**
- ✓ G-CSF is reserved for risky patients.
- ✓ **GM**-CSF **also reduces** the duration of neutropenia after cytotoxic chemotherapy. It has been more difficult to show that GM-CSF reduces the incidence of febrile neutropenia, probably because GM-CSF itself **can induce fever.**
- ✓ They are safe even in the post-chemotherapy supportive care of patients with acute myeloid leukemia (AML).

Other clinical applications of myeloid growth factors include congenital neutropenia, cyclic neutropenia, myelodysplasia, and aplastic anemia.

These factors are also used in the following procedures to restore the function of the bone marrow:

1) Autologous stem cell transplantation:

- ✓ High dose chemotherapy regimens produce extreme myelosuppression, which is counteracted by **reinfusion** of the patient's **own** hematopoietic stem cells which are collected before the chemotherapy.

2) Allogenic bone marrow transplantation:

- ✓ For treatment of **hematologic malignancies** or **bone marrow failure** states.
  In this setting, the growth factors speed the recovery from neutropenia without increasing the incidence of **acute graft-versus-host disease**.

3) Mobilization of peripheral blood stem cells (PBSCs): (discussed briefly in the previous page)

- ✓ Patients or donors are given GM-CSF for 4 days, then they do blood leukapheresis (separating out WBCs of blood and returning the remainder to the circulation), **CD34** is used as a marker for the stem cells. At least $5x10^6$ CD34 cells/Kg should be reinfused to ensure effective engraftment.

Toxicity of myeloid growth factors:

- ✓ **Bone pain.**
- ✓ **Fever, malaise, arthralgia and myalgia .**
- ✓ **Capillary Leak Syndrome: peripheral edema, pleural or pericardial effusions.**
- ✓ **Allergic reactions.**
- ✓ **Splenic rupture.**

3) Megakaryocyte Growth Factors:

A) Interleukin – 11 (IL – 11):

- ✓ 65-85 kDa protein.
- ✓ Produced by **fibroblasts and stromal cells** in the bone marrow .
- ✓ Half-life: 7-8 hours after **SC** injection.
- ✓ Acts through specific receptor.
- ✓ Stimulates the growth of multiple **lymphoid** and **myeloid** cells.
- ✓ Stimulates the growth of **primitive megakaryocytic progenitors**.
- ✓ Increases the number of peripheral **platelets** and **neutrophils**.

- **Clinical applications (uses):**
  - ✓ In thrombocytopenia; platelets transfusion is an older less practical alternative.
  - ✓ Patients with congenital thrombocytopenia require frequent treatment.
  - ✓ Approved for the secondary prevention of thrombocytopenia in patients receiving cytotoxic chemotherapy for treatment of **non-myeloid** cancers.

B) Oprelvekin:

- ✓ It is the recombinant form of IL-11.
- ✓ Produced by expression in E.coli.

C) Thrombopoietin (discovered in 2008):

- ✓ 65-85 kDa glycoprotein.
- ✓ Recombinant form is produced by expression in **human cells.**
- ✓ ***Eltrombopag*** and ***Romiplostim*** (thrombopoietin agonists) independently stimulate the growth of primitive megakaryocytic progenitors. They can also stimulate mature megakaryocytes and activates mature platelets to respond to aggregation by inducing certain stimuli.

Toxicity of megakaryocyte growth factors include:-

- ✓ **Fatigue, headache, dizziness, anemia, dyspnea, transient atrial arrhythmias and hypokalemia.**