

- Pharma 2 sum. | Done by: Ola Alahdab

1) Hematopoietic Growth Factors: Erythropoietin, (CSFs), (G-CSF), (GM-CSF), (IL-11), Thrombopoietin

- **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

- **Darbepoetin alfa** (modified form of erythropoietin) has longer half-life than epoetin alfa.

Erythropoietin's indications	Dose (not for memorizing)	Notes
1- Anemia of chronic renal failure (Deficiency of erythropoietin) <i>CRF</i>	Usually small doses are sufficient; (50-150 IU/Kg) IV or SC (subcutaneously) 3 times a week.	<ul style="list-style-type: none"> ✓ 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).	<ul style="list-style-type: none"> ✓ 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- Unethically, 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).

- Side effects of erythropoietin: hypertension & thrombotic complications, due to rapid increase in hematocrit & hemoglobin.

2) Myeloid Growth Factors:

- **rHuG-CSF "Filgrastim"**: 175 amino acids (not glycosylated).

- Produced in a bacterial cell expression system.

- **Pegfilgrastim**:

✓ it's covalently conjugated with polyethylene glycol (PEG) to increase the duration of action.

- It has much longer half-life than rHuG-CSF.

- It can be injected once per chemotherapy cycle.

- **rHuGM-CSF "Sargramostim"**: 127 amino acids.

- Produced in a yeast cell expression system.

- Half-life: 2-7 hours.

A) G-CSF:-

✓ Works on JAK/STAT receptors on WBC progenitors.

✓ Stimulates neutrophil lineage.

✓ Activates the phagocytic activity of mature neutrophils & prolongs their survival.

✓ Mobilizes hematopoietic stem cells into the peripheral circulation, helpful in **transplantation**; the use of peripheral blood stem cells (PBSCs) rather than bone marrow stem cells for autologous & allogeneic hematopoietic stem cell transplantation.

B) GM-CSF:-

✓ Has broader actions than G-CSF, also works on (JAK/STAT receptors).

✓ Stimulates granulocytic progenitor cells, erythroid, & megakaryocyte progenitors.

✓ Acts 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.

- Uses of myeloid growth factors:

1) Cancer chemotherapy-induced neutropenia:

- G-CSF accelerates neutrophil recovery after cancer chemotherapy, leading to reduced episodes of febrile neutropenia, but it doesn't improve survival.

- GM-CSF also reduces neutropenia duration after cytotoxic chemotherapy. (It is 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)**.

*granulocyte transfusion is not practical due to their short life-span.

- **We Restore bone marrow function by:**

A- Autologous stem cell transplantation: **reinfusion** of patient's own hematopoietic stem cells which are collected before the chemotherapy

B- Allogenic bone marrow transplantation: to treat **hematologic malignancies** or **bone marrow failure**, In this setting, the growth factors speed the recovery from neutropenia without increasing the incidence of **acute graft-versus-host disease**.

C- Mobilization of peripheral blood stem cells (PBSCs). By giving GM-CSF for 4 days, to induce blood leukapheresis (separating WBCs of blood & returning the remainder to the circulation), **CD34** is the marker for the stem cells.

2) Congenital neutropenia 3) Cyclic neutropenia 4) Myelodysplasia 5) Aplastic anemia

- Side effects:

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

3) Megakaryocyte Growth Factors:

A) Interleukin – 11 (IL – 11):

- Produced by bone marrow fibroblasts & stromal cells.

- Half-life: 7-8 hours (SC injection).

- Stimulates growth of multiple lymphoid, myeloid cells, & primitive megakaryocytic progenitors.

✓ Increases the number of peripheral platelets & neutrophils.

- uses:

1) **Thrombocytopenia**. *platelets transfusion is an older less practical alternative.

2) **Congenital thrombocytopenia** require frequent treatment.

3) **Secondary prevention of thrombocytopenia** in patients receiving cytotoxic **chemotherapy** for treatment of non-myeloid cancers.

B) Oprelvekin:

- The recombinant form of **IL-11**, produced by expression in E.coli.

C) Thrombopoietin: (a glycoprotein).

- Recombinant form is produced by expression in human cells.

- **Eltrombopag & Romiplostim** (thrombopoietin agonists) **independently** stimulate the growth of primitive megakaryocytic progenitors & stimulate the mature megakaryocytes & activates mature platelets to respond to aggregation by inducing certain stimuli.

- Side effects:

Fatigue | headache | dizziness | anemia | dyspnea | transient atrial arrhythmias | hypokalemia