

 Hematopoietic Growth Factors
 Regulate the proliferation and differentiation of hematopoietic progenitor cells in the bone marrow.

Useful in hematologic as well as nonhematologic conditions.
Potential anticancer and antiinflammatory drugs.

# Hematopoietic Growth Factors Erythropoietin (Epoetin alfa).

#### Colony Stimulating Factors:

- Granulocyte colony-stimulating factor(G-CSF).
- Granulocyte-macrophage colony-stimulating factor (GM-CSF).

# Interleukin-11 (IL-11).Thrombopoietin.

- 34-39 kDa glycoprotein.
- Was the first isolated growth factor.
- Originally purified from urine of patients with severe anemia.
- Recombinant human erythropoietin (rHuEPO, or Epoietin alfa) is produced in a mammalian cell expression system.
- Half-life after iv administration is 4-13 hours.
- It is not cleared by dialysis.
- Darbepoetin alfa has longer half life. October 15

# Erythropoietin Produced in the kidney in response to hypoxia through increased rate of transcription of the gene . Needs active bone marrow (no deficiency, no primary bone marrow disease and no book and no b

suppression by drugs or chronic diseases).

Elevated in most of anemias (up to thousands) but lowered in anemia of chronic renal failure.

# Erythropoietin Stimulates erythroid proliferation and differentiation by interacting with specific receptor( JAK/STAT cytokine receptor) on red cell progenitor. Releases reticulocytes from the

#### bone marrow.

#### **Indications:**

## 1. Anemia of chronic renal failure:

These are the patients most likely to benefit from treatment.
50-150 IU/kg IV or SC three times a week.

-Failure to respond is usually due to iron or folic acid deficiency.

**Indications:** 

#### 2. <u>Primary bone marrow disorders and</u> <u>secondary anemias</u>:

 Aplastic anemia, myeloproliferative and myelodysplastic disorders, multiple myeloma and bone marrow malignancies. Also anemia of chronic inflammation, AIDS and cancer.

Response is generally incomplete.

Response is better with low baseline erythropoietin levels.

- Patients require higher doses(100-500 Munir Gharaibeh MD, PhD, MHPE

#### **Indications:**

- 3. Anemia of zidovudine treatment.
- 4 Anemia of prematurity.
- 5. After phlebotomies for autologous transfusion for elective surgery.
- 6. Iron overload.
- 7. Unethically, used by athletes.

#### **Toxicity:**

 Due to rapid increases in hematocrit and hemoglobin: hypertension and thrombotic complications.
 Allergic reactions are infrequent and mild.

**Myeloid Growth Factors** rHuG-CSF"Filgrastim"(1991): Works on JAK/STAT receptors. 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 hemopoietic stem cells into the peripheral circulation.

October 15

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# Myeloid Growth Factors <u>rHuGM-CSF"Sargramostim"</u>:

- Has broader actions. Also works on JAK/STAT receptors.
- Stimulates proliferation and differentiation of early and late granulocytic progenitor cells as well as erythroid and megakaryocyte progenitors.
- With interleukin-2, also stimulates 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** 

#### <u>Cancer Chemotherapy-Induced</u> <u>Neutropenia:</u>

- Granulocyte transfusion is not practical.
- G-CSF accelerates neutrophil recovery, leading to reduced episodes of febrile neutropenia, need for antibiotics and days of hospitalization, but do not improve survival.
- G-CSF is reserved for risky patients.
- GM-CSF can produce fever on its own.

They are safe even in the postchemotherapy supportive care of patients with AML. **Other Applications of Myeloid Growth Factors** 

- Congenital neutropenia.
- Cyclic neutropenia.
- Myelodysplasia.
- Aplastic anemia.
- Autologous Stem Cell Transplantation.
- Allogenic Bone Marrow Transplantation.
- Mobilization of peripheral blood stem cells (PBSCs).

## **Toxicity of Myeloid Growth Factors**

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

# Megakaryocyte Growth Factors Interleukin-11 (IL-11):

- Physiological factor.

#### Oprelvekin:

- Is the recombinant form.
- Produced by expression in E.coli.

**Megakaryocyte Growth Factors** Interleukin-11 (IL-11): -Acts through a 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.

**Megakaryocyte Growth Factors <u>Clinical Applications:</u>** Thrombocytopenia Platelets transfusion is an alternative. Approved for the secondary prevention of thrombocytopenia in patients receiving cytotoxic chemotherapy for treatment of nonmyeloid cancers.

## Megakaryocyte Growth Factors <u>Thrombopoietin:</u>

 Still an investigational agent. - Recombinant form is produced by expression in human cells. -Independently stimulates the growth of primitive megakaryocytic progenitors. -Also stimulates mature megakaryotes. - Activates mature platelets to respond to aggregation-inducing stimuli.