

# Hematopoietic Growth Factors

- Erythropoietin (Epoetin alfa).
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- Granulocyte colony-stimulating factor(G-CSF).
- Granulocyte-macrophage colony-stimulating factor (G-CSF).
- Interleukin-11 (IL-11).
- Thrombopoietin.

# **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.**

# Erythropoietin

- 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.

# 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 suppression by drugs or chronic diseases).
- Normal serum level 20 IU/L.
- 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 receptors( JAK/STAT cytokine receptor) on red cell progenitor.
- Releases reticulocytes from the bone marrow.

# Erythropoietin

## 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.

# Erythropoietin

## Indications:

- **2. Primary bone marrow disorders and secondary anemias:** aplastic anemia, myeloproliferative and myelodysplastic disorders, multiple myeloma and bone marrow malignancies. Also anemia of chronic inflammation, AIDS and cancer.
  - Response is better with low baseline erythropoietin levels.
  - Patients require higher doses(100-500 IU/kg).
  - Response is generally incomplete.

# Erythropoietin

## 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.



# Erythropoietin

## Toxicity:

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

# Myeloid Growth Factors

- Originally purified from cultured human cells.
- rHuG-CSF “Filgrastim” 1991:
  - Produced in a bacterial cell expression system.
  - 175 amino acids, 18 kD mol. wt.
  - Has a half life of 2-7 hours.
  - Pegfilgrastim= Filgrastim covalently conjugated with polyethylene glycol. Injected once per chemotherapy cycle.

# Myeloid Growth Factors

## rHuGM-CSF “Sargramostim”:

- Produced in a yeast cell expression system.
- 127 amino acids, 15-19 kD mol. wt.
- Has a half life of 2-7 hours.

# Myeloid Growth Factors

## G-CSF:

- 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.

# Myeloid Growth Factors

## GM-CSF:

- 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

### Cancer Chemotherapy-Induced Neutropenia:

- 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.

# Clinical Applications of Myeloid Growth Factors

- **Congenital neutropenia.**
- **Cyclic neutropenia.**
- **Myelodysplasia.**
- **Aplastic anemia.**

# Clinical Applications of Myeloid Growth Factors

## 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.

## ● Allogenic Bone Marrow Transplantation.

## ● Mobilization of peripheral blood stem cells (PBSCs).

- Patients or donors are given GM-CSF (5-10 mcg/kg/day) for 4 days, then leukapheresis, CD34 is used as a marker for the stem cells. At least  $5 \times 10^6$  CD34 cells/kg should be reinfused to ensure effective engraftment.



# 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):

- 65-85 kDa protein.
- Produced by fibroblasts and stromal cells in the bone marrow.
- Half life is 7-8 hours after sc injection.

- 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

## Clinical Applications of IL-11:

- **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

## Clinical Applications of IL-11 :

- Does not appear to have an effect on leukopenia caused by myelosuppressive chemotherapy.
- Given by SC injection, 50mcg/kg/day for 2-3 weeks after chemotherapy. Or, until platelet count rises to  $<50,000$  cells/ $\mu$ l.

# Megakaryocyte Growth Factors

## Thrombopoietin:

- It is still an investigational agent.
- 65-85 kDa glycoprotein.
- 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

# Megakaryocyte Growth Factors

## Toxicity:

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