Hematopoietic Growth Factors

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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 (G-CSF).
- Interleukin-11 (IL-11).
- Thrombopoietin.
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.
Indications of Erythropoietin

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 of Erythropoietin

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.
Indications of Erythropoietin


4. Anemia of prematurity.

5. After phlebotomies for autologous transfusion for elective surgery.


7. Unethically, used by athletes.
Toxicity of Erythropoietin

- 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 post chemotherapy 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

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. Allogeneic Bone Marrow Transplantation.

3. Mobilization of peripheral blood stem cells (PBSCs).
   - Patients or donors are given GM-CSF 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.
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/µl.
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 megakaryocytes.
- Activates mature platelets to respond to aggregation-inducing stimuli.
Toxicity:
- Fatigue, headache, dizziness, anemia, dyspnea, transient atrial arrhythmias and hypokalemia.