Pharmacology - HLS

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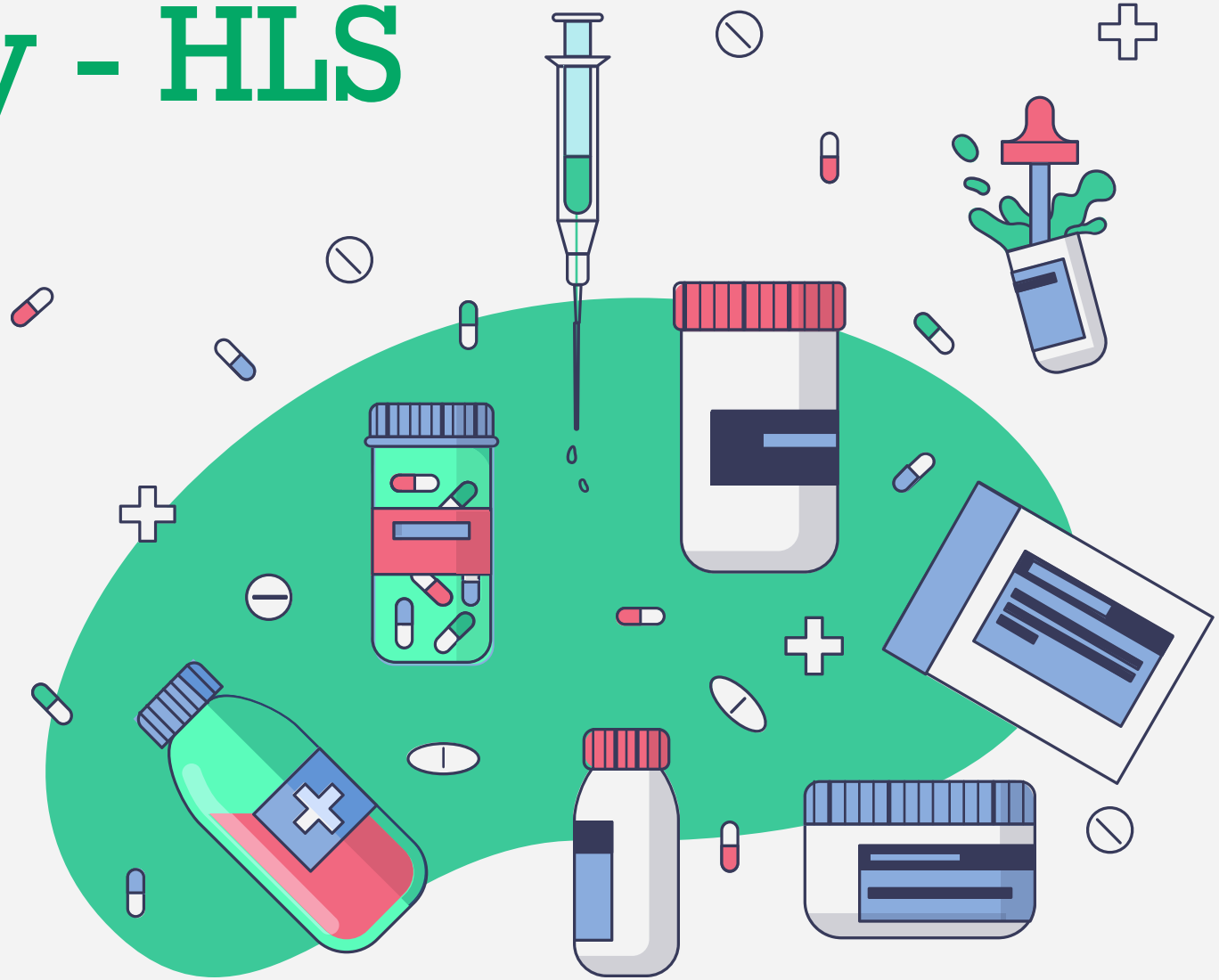

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Hematopoietic Growth Factors

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Hematopoietic Growth Factors

- **Regulate the proliferation and differentiation of hematopoietic progenitor cells in the bone marrow.** **(MAIN USE FOR THESE FACTORS)**

- **Useful in hematologic as well as non-hematologic conditions, potential anticancer and anti-inflammatory 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.**

- **These affect RBCs, WBCs as well as platelets.**

Erythropoietin

- 34-39 kDa glycoprotein.(large molecule)
- Was the first(1977) isolated growth factor.
- Originally purified from urine of patients with severe anemia.(Not a practical way of obtaining erythropoietin nowadays)
- Recombinant human erythropoietin (rHuEPO, or Epoetin alfa) is produced in a mammalian cell expression system.
- Half-life after iv administration is 4-13 hours.(relatively short half-life)
- 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 [healthy 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.(Normal production of erythropoietin depends on the presence of good renal activity)**

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.**

(activates the production of RBCs and can be used in certain treatments of anemia)

Indications of Erythropoietin

- **1. Anemia of chronic renal failure:**
- **The Cause of this anemia is deficiency of erythropoietin.**

  - **These are the patients most likely to benefit from treatment.**
  - **50-150 IU/kg IV or SC three times a week. [small doses are sufficient]**
  - **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.[more effective]**
  - **Patients require higher doses(100-500 IU/kg).**
  - **Response is generally incomplete.[problem is not mainly caused by deficiency of erythropoietin]**

Indications of Erythropoietin

- **3. Anemia of zidovudine treatment.** **[zidovudine:anti-viral agent]**
- **4 Anemia of prematurity.** **[underdevelopment of BM , stimulated by giving erythropoietin]**
- **5. Iron overload.** **[toxicity due to IV adminstration of iron, erythropoietin is given to stimulate BM in order to consume iron in the bone marrow, reducing iron concentrations in the blood]**
- **6. 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.** **[produced by recombinant DNA technology]**

Granulocyte Colony Stimulating Factors

- **Originally purified from cultured human cells.** **[not practical because WBCs have short-life span so quantities purified could be minimal]**
- **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 [increases the duration of action for filgrastim]. Injected once per chemotherapy cycle. (relatively longer half-life)**

Granulocyte Colony Stimulating Factors

- **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.**

Granulocyte Macrophage Colony Stimulating 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.**

Granulocyte Macrophage Colony Stimulating Factors

- **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:

- **Neutropenia: low level of neutrophils and high susceptibility for infections.**

❖**Granulocyte transfusion is not practical.** **[isolation of granulocytic WBCs from donated blood,BUT WBCs have short life-span which made it unsuccessful]**

- **G-CSF accelerates neutrophil recovery, leading to reduced episodes of febrile neutropenia, need for antibiotics and days of hospitalization , but do not improve survival.** **[patients mostly die from chemotherapy rather than the cancer itself by secondary infections due to suppression of BM and neutrophils or WBCs]**
- **G-CSF is reserved for risky patients.**
- **GM-CSF can produce fever on its own.** **[confuses the condition]**
- **They are safe even in the post chemotherapy supportive care of patients with AML.**

Other Clinical Applications of Myeloid Growth Factors

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

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**

- **Approved for the secondary prevention of thrombocytopenia in patients receiving cytotoxic chemotherapy for treatment of nonmyeloid cancers.**

- **Platelets transfusion is an alternative.** **[less practical , platelets preparation is difficult , transfusing blood carry many risks such as ; blood overloading the circulation or contaminated transfused blood]**

Megakaryocyte Growth Factors

Thrombopoietin(2008):

-65-85 kDa glycoprotein.
-Recombinant form is produced by expression in human cells.
-Eltrombopag
-Romiplostim
-Independently stimulates the growth of primitive megakaryocytic progenitors.
-Also stimulates mature megakaryocytes.
-Activates mature platelets to respond to aggregation-inducing stimuli.

Megakaryocyte Growth Factors

Toxicity:

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