Hematopoietic Growth Factors

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Hematopoietic Growth Factors

- Regulate the proliferation and differentiation of hematopoietic progenitor cells in the bone marrow. (They enhance / stimulate hematopoietic stem cells in the bone marrow)

FORTUNATELY, ↴

- Useful in hematologic as well as nonhematologic conditions, potential anticancer and antiinflammatory drugs.

Hematopoietic Growth Factors

- Erythropoietin (Epoetin alfa). (well Known and old factor)
- Colony Stimulating Factors.
- Granulocyte colony-stimulating factor(G-CSF).
- Granulocyte-macrophage colony-stimulating factor (GM-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.

this means that patients with severe anemia have high levels of erythropoietin.

~more recent discovery/new technology making erythropoietin easily available, long time ago they used to extract it from the urine of anemic patients.

* (since produced in the kidney)

(given less frequently)

relatively short half-life and must be given on a daily basis (unfavorable, impractical, and patient's compliance is negligible)

Erythropoietin

anaemia causes hypoxia which stimulates the bone marrow as well as the kidneys. The kidneys will produce more erythropoietin } thus more erythrocytes.

- Produced in the kidney in response to hypoxia through increased rate of transcription of the gene. (thus excreted via the urine)
- Needs active bone marrow (no deficiency, no primary bone marrow disease and no suppression by drugs or chronic diseases). active = healthy * the existence of healthy bone marrow depends on the presence of the following elements:
  - iron
  - vitamin B12
  - folic acid
  - absence of primary bone marrow disease (eg. leukemia)
  - absence of drugs causing bone marrow suppression.
- Normal serum level 20 IU/L. (20 international units/litre)
- Elevated in most of anemias (up to thousands) but lowered in anemia of chronic renal failure. (less than 20 IU/L)

← note: patients with chronic kidney disease/ chronic renal failure will have ↓ production of erythropoietin and this leads to a special type of anaemia that doesn't respond to iron } vit. B12 supplements. (anemia due to deficiency of erythropoietin)

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. → which go into the circulation and differentiate into mature RBCs.

Indications of Erythropoietin

- 1. Anemia of chronic renal failure: (most logical indication for erythropoietin ~ problem in its production center AKA → kidneys)
  - 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.

(if the primary elements needed for erythropoiesis aka iron, folic acid, etc... then stimulating the bone marrow using erythropoietin would be useless)

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. (Bone marrow could be suppressed by these conditions)

  - Response is better with low baseline erythropoietin levels. (so we work on giving erythropoietin to ↑ these baseline levels)
  - Patients require higher doses(100-500 IU/kg). → (bone marrow is weak in this indication, in the 1st indication 'Anemia of chronic renal failure', the problem was in the kidney not in the bone marrow, that's why this indication requires a higher dose)
  - Response is generally incomplete. (there is some abnormality in the bone marrow so it will not respond as much, compared to the response in renal failure (1st indication) which is considered to be very potent.)

Indications of Erythropoietin

- 3. Anemia of zidovudine treatment. → (zidovudine is an anti-viral drug used in Hepatitis)
- 4 Anemia of prematurity. (anaemia affecting preterm infants, don't have mature bone marrow, erythropoietin can be used to encourage b.m.)
- 5. After phlebotomies for autologous transfusion for elective surgery.
- 6. Iron overload.
- 7. Unethically, used by athletes.

→ phlebotomy: withdrawing blood.
→ autologous transfusion: collection of blood from a single patient and retransfusion back to the same patient when required.

- the need of more O_2, more RBCs → erythropoietin will stimulate the b.m → ↑ RBCs → ↑ athelets' ENDURANCE.

- give Deferoxamine as mentioned in previous lecture, BUT can also be given erythropoietin to stimulate the use of this excess iron in the production of RBCs. (preventig iron toxicity)

- After withdrawing blood (1-2 Litres), one or two months prior to surgery, this patient may develop anemia, so they are given erythropoietin in order to stimulate the bone marrow. (↑RBC production) The blood withdrawn is later retransfused to the same patient after the surgery.

Toxicity of Erythropoietin

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

• caused by :- ↑ blood volume or ↑ specific graviy of blood

(↑ in erythropoietin leads to an ↑ in RBCs leading to polycythemia)

↱ target mainly WBCs!

Myeloid Growth Factors

- Originally purified from cultured human cells. ~ not WBCs taken from urine, or blood because their half lives are very short (hrs to days)
- 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. → to ↑ duration of action, PEG ↗ is an inert organic solvent.

- recombinant human Granulocyte colony Stimulating factor also known as 'filgrastim'.
- filgrastim is the first growth factor produced by gene technology in 1991, in E. coli cell expression system.

- Chemotherapy leads to:
  - bone marrow suppression, myelosuppression, and neutropenia.
- So we need more WBCs to compensate for their loss in chemotherapy, and thus we give 'Pegfilgrastim'.

Myeloid Growth Factors

rHuGM-CSF "Sargramostim": recombinant Human granulocyte macrophage CSF.

- 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. like erythropoietin.
- 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.

→ focuses on neutrophils manufacture, production, and release.

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. (has a wider application compared to G-CSF)
- 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.

* G-CSF is more specific towards neutrophils while GM-CSF has a broader activity. (less specificity)

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.

We can't get granulocytes and give them directly to patients, so solution is Myeloid Growth factors!

(improves morbidity but not mortality)

antibiotics & hospitalization are needed to ↑ immunity.

can also caused by infection. So, we have to make sure: is the fever from infection or from G-M-CSF?

(Acute Myeloid Leukemia)

* Chemotherapy effects neutrophils in particular would cause severe disabilities.
* problems in immunity arise, ↑ risk of infections. (patients are thus isolated)

Clinical Applications of Myeloid Growth Factors

* These conditions are minor indications but worth a try to be treated with Myeloid GFs.

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

This is just for clarification:

Severe congenital neutropenia is a condition that causes affected individuals to be prone to recurrent infections. People with this condition have a shortage (deficiency) of neutrophils.

Cyclic neutropenia is a rare blood disorder characterized by recurrent episodes of abnormally low levels of neutrophils (a type of white blood cell) in the body.tends to occur approximately every three weeks and lasting for few days at a time due to changing rates of neutrophil production by the bone marrow.

Myelodysplastic syndromes (MDS) are a group of cancers in which immature blood cells in the bone marrow do not mature and therefore do not become healthy blood cells.

Aplastic anemia is an autoimmune disease in which the body fails to produce blood cells in sufficient numbers. Aplastic anaemia causes a deficiency of all blood cell types: red blood cells, white blood cells, and platelets.

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. Allogenic Bone Marrow Transplantation.

→ using healthy blood stem cells from a donor eg. close relative.

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 5x10^6 CD34 cells/kg should be reinfused to ensure effective engraftment.

lab procedure in which WBCs are seperated from the blood.

Autologous stem cell transplantation:

- Taking blood from a patient before chemotherapy then isolating their stem cells. Giving patient Chemotherapy → leading to bone marrow suppression → then giving back the patient their stem cells & stimulating these stem cells via granulocyte & growth factors. (Stem cells can also be taken from the umbilical cord & stored for later therapy once the baby is born)

Toxicity of Myeloid Growth Factors

- Bone pain. (of the long bones with active bone marrow)
- Fever, malaise, arthralgia, myalgia.
- Capillary Leak Syndrome: peripheral edema, pleural or pericardial effusions.
- Allergic reactions.
- Splenic rupture.

(Spleen is responsible for blood filtration, due to accumulation of old cells, etc... might lead to rupture.)

(defects in capillaries)

CLARIFICATION:

- Systemic capillary leak syndrome (SCLS) is a condition in which fluid and proteins leak out of tiny blood vessels, into surrounding tissues . This can result in dangerously low blood pressure (hypotensison), hypoalbuminemia, and a decrease in plasma volume (hemoconcentration).
- In medical terminology, an effusion refers to accumulation of fluid in an anatomic space, usually without loculation.

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. (not only megakaryocytes)
  - 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. (Remember we can do RBC transfusions & Platelet transfusions BUT NOT WBC transfusions)

  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.

everyday for 2-3 weeks

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.

Stimulates mature platelets as well as immature platelets ...

Megakaryocyte Growth Factors

Toxicity:

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