ORIGINAL RESEARCH PAPER

Pharmacology

MYELOID GROWTH FACTORS: A REVIEW

KEY WORDS:

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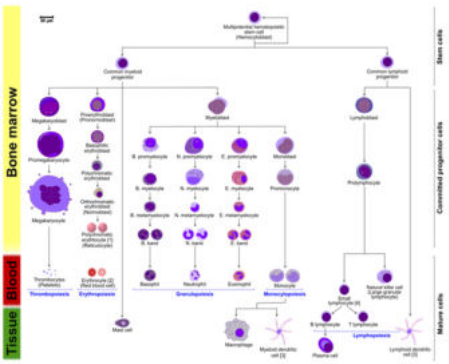
HEMATOPOEISIS AND HEMATOPOEITIC STEM CELLS (HSC)

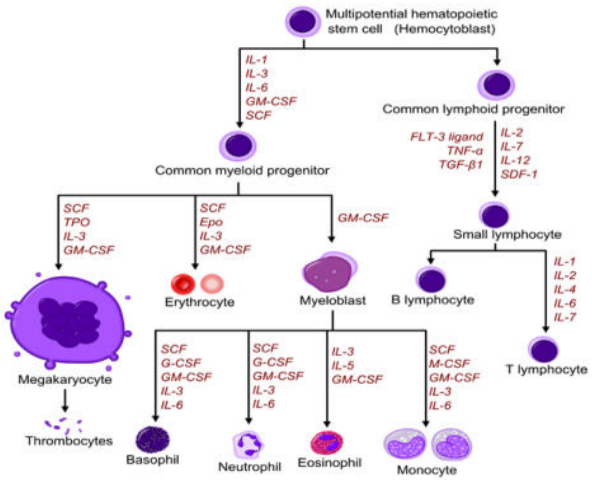
Haematopoiesis is the process by which blood cells are formed. The process occurs in embryonic development and throughout adulthood to produce and replenish the blood system. The site of haematopoiesis changes according to the age. In developing embryos, blood formation occurs in aggregates of blood cells in the yolk sac, called blood islands. As development progresses, blood formation occurs in the spleen, liver and lymph nodes. When bone marrow develops, it eventually assumes the task of forming most of the blood cells for the entire organism.[2] However, maturation, activation, and some proliferation of lymphoid cells occurs in the spleen, thymus, and lymph nodes. In children, haematopoiesis occurs in the marrow of the long bones such as the femur and tibia. In adults, it occurs mainly in the pelvis, cranium, vertebrae, and sternum.[3] In a healthy adult person, approximately 10^{11}–10^{12} new blood cells are produced daily in order to maintain steady state levels in the peripheral circulation.[3]

The process of haematopoiesis requires haematopoietic stem cells. Haematopoietic stem cells are the multipotent cells which gives rise to all the blood cell. In humans, the very first HSCs arise from the ventral endothelial wall of the embryonic aorta within the aorta-gonad-mesonephros region, through a process known as endothelial to haematopoietic transition. [[4] HSCs are found in the bone marrow of adults, especially in the pelvis, femur, sternum. They are also found in umbilical cord blood and peripheral blood. HSCs gives rise to different types of blood cells, in lines called myeloid and lymphoid.[5] HSCs are round, non-adherent, with a rounded nucleus and low cytoplasm-to-nucleus ratio. In shape, hematopoietic stem cells resemble lymphocytes. It is difficult to identify them under microscope. They can be identified by Flow cytometry because HSCs have CD34 antigen on their surface which is lost as they differentiate into lineage specific blood cell precursors. Hence CD34 can be used as biomarker for identifying and collecting HSCs during haematopoietic stem cell transplantation. HSCs have two very important properties, differentiation and self-renewal. One HSC when divides, it divides into two daughter cells. One daughter cell remains as HSC i.e., self-renewal while the other daughter cell differentiates further into either myeloid progenitor cell or lymphoid progenitor cell. Myeloid progenitor cell can eventually differentiate into either erythrocyte, platelet, leukocyte or mast cell and lymphoid progenitor cell can eventually differentiate into B lymphocyte, T lymphocyte or NK cell.



HEMATOPIETIC GROWTH FACTORS

Hematopoietic growth factors are a family of regulatory molecules that play important roles in the growth, survival, and differentiation of blood progenitor cells, as well as in the functional activation of mature cells.[6] The commercial availability of these recombinant human hematopoietic growth factors has led to their wide clinical application in oncology practice. Hematopoietic and lymphopoietic growth factors are glycoproteins produced by a number of marrow cells and peripheral tissues. They are active at very low concentrations and typically affect more than one committed cell lineage. Different haematopoietic growth factors include Erythropoietin, Thrombopoietin, Stem cell factors, Interleukins, myeloid growth factors. Erythropoietin stimulates proliferation and maturation of committed erythroid progenitors to increase red cell production. Stem cell factors act synergistically with wide range of other growth factors and interleukins to stimulate committed and noncommitted stem cells. Thrombopoietin stimulates stem cell differentiation into megakaryocyte progenitors and increases production of platelets. Myeloid growth factors increase production and enhances function of leukocytes.[7]



MYELOID GROWTH FACTORS:

Myeloid growth factors (MGFs) are a class of biologic agents that regulate the proliferation, differentiation, survival, and activation of cells in the myeloid lineage. Myeloid growth factors are produced naturally by a number of different cells, including fibroblasts, endothelial cells, macrophages, and T cells. These factors are active at extremely low concentrations and act via membrane receptors of the cytokine receptor superfamily to activate the Jak/STAT signal transduction pathway.**[7]** They are also called as colony stimulating factors. Different MGFs are Granulocyte colony stimulating factor (G-CSF), Monocyte colony stimulating factor(M-CSF), Granulocyte Macrophage colony stimulating factor (GM-CSF). G-CSF acts on neutrophil while M-CSF acts on monocyte by increasing their production and enhancing their action. GM-CSF has wider biological action. It acts on early and late granulocyte progenitors as well as erythroid and megakaryocytic progenitor cells, so increases production of

RBC, WBC as well as platelets. GM-CSF also enhances the migration, phagocytosis, superoxide production, and antibody-dependent cell-mediated toxicity of neutrophils, monocytes, and eosinophils. G-CSF reduces inflammation by inhibiting IL-1, tumour necrosis factor, and interferon gamma. G-CSF and GM-CSF also mobilizes primitive hematopoietic stem cells, from the marrow into the peripheral blood (Sheridan et al., 1992). This observation has virtually transformed the practice of stem cell transplantation, such that more than 90% of all such procedures today use G-CSF–mobilized peripheral blood cells as the donor stem cell product. MGFs are Effective in extremely low concentration (10^{-12} to 10^{-10} mMol/lit). MGF are produced by fibroblasts, endothelial cells, T cells, macrophages. Recombinant forms of several myeloid growth factors have been produced although only G-CSF and GM-CSF found to have meaningful clinical application.[7]

Recombinant G-CSF is Filgrastim, Peg filgrastim, Lenograstim while recombinant GM-CSF are Sargramostim, Molgramostim.

RECOMBINAT G-CSF

Filgrastim is a glycoprotein with 175 amino acids. It is obtained from E. coli. It specifically increases the production and function of neutrophils.it is excreted by renal route. Pegfilgrastim is a pegylated version of filgrastim, which increase the molecular weight of molecule which is not suitable for renal excretion. Hence pegfilgrastim is longer acting form of filgrastim with plasma half-life of 15 to 80 hours.[8] Other properties are mostly similar to filgrastim. Lenograstim is glycosylated filgrastim. It is found to mobilize a greater number of stem cell in peripheral blood in healthy individual. [7]Filgrastim is on WHO's list of essential medicines[9]

ACTIONS:

actions of filgrastim and pegfilgrastim are almost similar. They increase the production of Neutrophils.[10][11] They increase the functions of neutrophils like migration, phagocytosis, superoxide production, antibody-dependent cell-mediated toxicity. By increasing the production, they also decrease the period of neutropenia that commonly occur after myelosuppressive chemotherapy. They mobilize HSCs from bone marrow to peripheral blood which is key for collecting HSCs for haematopoietic stem cell transplantation.[7]

INDICATIONS:

major indication of recombinant G-CSF is preventing or correcting neutropenia caused by various reasons like myelosuppressive chemotherapy, congenital neutropenia, neutropenia in advanced AIDS, neutropenia caused by Zidovudine. These drugs are commonly used before haematopoietic stem cell transplantation for collecting peripheral blood stem cells.

DOSAGE AND ROUTE OF ADMINISTRATION:

They can be given by either iv or SC route. Subcutaneous route is the preferred route. For neutropenia after chemotherapy filgrastim is given in dose of 1 to 20 micrograms/kg daily, mostly 5 microgram/kg. It should be started within 24 to 72 hours after the cycle of chemotherapy and should be continued till the absolute neutrophil count reaches >10000/ul. Next cycle of chemotherapy should not be started within 24 hours of the last dose. For peripheral blood stem cell collection, it is given in dose of 5 to 10 ug/kg daily for 4 days and leukapheresis is done on 5th day. Pegfilgrastim is given as a fixed single dose of 6mg within 24 to 72 hours of cycle.[7]

SIDE EFFECTS AND CONTRAINDICATION:

Nausea, vomiting is commonly seen. Bone pain or exacerbation of arthritic symptoms can be seen in 20-30 % patients. Injection site side effects can occur after subcutaneous injection. Very rarely splenomegaly and splenic rupture is seen. Hence patient presenting with left epigastric pain after these drugs should be evaluated. Both the drugs are obtained from E. coli therefore should be contraindicated in people with allergy for E. coli proteins. It is found that these drugs if given in sickle cell disease can precipitate the attack of sickle cell crisis. There is paucity of literature explaining the mechanism behind it. One commonly accepted theory is that these drugs increase the number of leukocytes and also increase the adhesion property which leads to vascular crisis in sickle cell disease.[12] Hence filgrastim should be avoided in patients with sickle cell disease.[7]

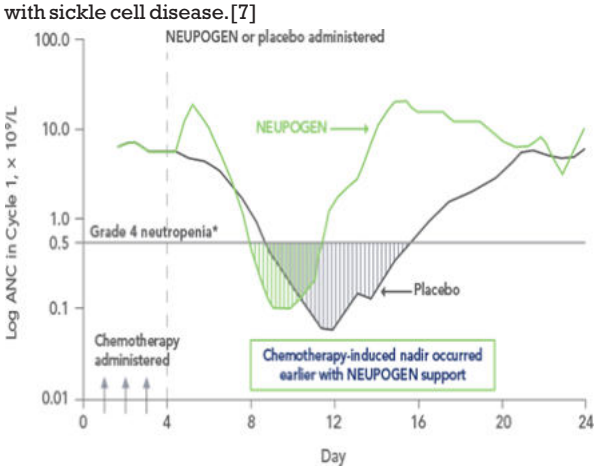


FIG:-The graph compares the effect of Filgrastim (Neupogen) and placebo on neutrophil count given after myelo suppressive chemotherapy. Filgrastim increases the nadir (lowest concentration of neutrophil after chemo) and decreases the total period of neutropenia.

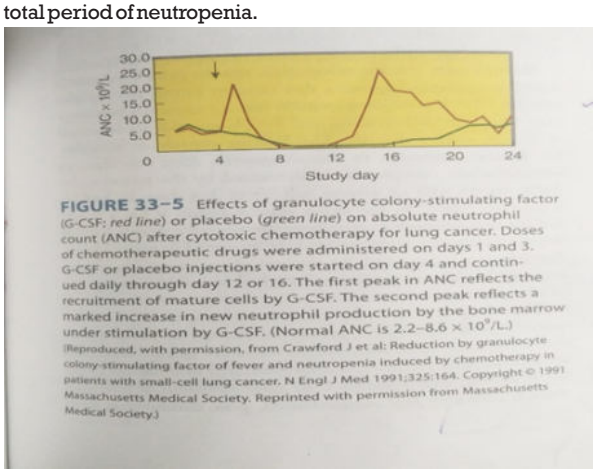


FIGURE 33–5 Effects of granulocyte colony-stimulating factor (G-CSF; *red line*) or placebo (*green line*) on absolute neutrophil count (ANC) after cytotoxic chemotherapy for lung cancer. Doses of chemotherapeutic drugs were administered on days 1 and 3. G-CSF or placebo injections were started on day 4 and continued daily through day 12 or 16. The first peak in ANC reflects the recruitment of mature cells by G-CSF. The second peak reflects a marked increase in new neutrophil production by the bone marrow under stimulation by G-CSF. (Normal ANC is 2.2–8.6 × 10^9/L.) (Reproduced, with permission, from Crawford J et al: Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 1991;325:164. Copyright © 1991 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

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RECOMBINANT GM-CSF

SARGRAMOSTIM: Sargramostim is recombinant GM-CSF. It is glycoprotein of 127 amino acid and is obtained from yeast.[14] Sargramostim increases the production of neutrophil at lower doses and monocyte, eosinophils at higher doses. Like filgrastim, it decreases the period of neutropenia after chemotherapy, increases the neutrophil function, and mobilize HSC to peripheral blood. It is used in dose of 250ug/m^2 subcutaneously or by iv infusion for post-chemotherapy neutropenia, PBSC collection and neutropenia after HSC transplantation. Sargramostim is also indicated in acute radiation exposure as 7ug/kg for an adult >40kg, as 10ug/kg in person of 15-40kg and as 12ug/kg in child <15kg.[7]

Common side effects include hypotension, tachycardia, flushing after first dose called as first dose effect which occur

only after first dose and not after subsequent doses. Less common side effects are mild flu like symptoms like fever, weakness, fatigue, headache. Very rare side effects include capillary leak syndrome which manifest as hypotension, hypoalbuminemia, swelling on body, pleural, pericardial effusion etc.

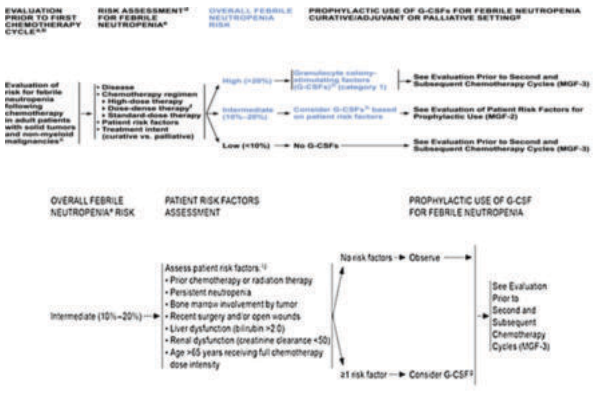
Two of the most significant use of MGFs are neutropenia after chemotherapy and PBSC collection for HSC transplantation.

1) USE OF MGFs FOR POST CHEMOTHERAPY NEUTROPENIA:

Almost all the chemotherapeutic agents have side effect of myelosuppression which leads to neutropenia. Neutropenia is defined as Absolute Neutrophil Count < 1500/ul. Severe neutropenia can also cause Febrile neutropenia which is defined as fever >38.3^{0c} and ANC < 500/ul or ANC<1000/ul which is predicted to fall below 500/ul in next 48 hours. National Comprehensive Cancer Network (NCCN) has given some guidelines for the use of G-CSF for prophylactic as well as therapeutic use in febrile neutropenia.[10]

PROPHYLACTIC USE OF G-CSFs

The risk of developing febrile neutropenia depends upon disease factors, chemotherapy regimen, patient risk factors, treatment intent. On the basis of these factors patient falls in high (>20%), intermediate (10-20%) or low(<10%) risk category. If the patient falls in high-risk category, prophylactic use of G-CSF is recommended. It is not advised if the patient falls in low-risk category. Patient falling in intermediate risk category should be dealt on individual considerations based of presence of patient risk factors like age>65 years, prior exposure to chemotherapy or radiotherapy, bone marrow involvement by tumour, recent surgery or open wounds etc. For patient having ≥1 of the above risk factors then G-CSF should be considered otherwise not.[10]



THERAPEUTIC USE OF G-CSFs

The NCCN panel recommends that patients presenting with FN who are receiving or have previously received prophylactic filgrastim should continue G-CSF. However, because pegfilgrastim are long-acting, patients who have received these agents prophylactically should not be treated with additional G-CSF.

For patients presenting with FN who have not received prophylactic G-CSF, the panel recommends an evaluation of risk factors for infection-related complications or poor clinical outcome. Features associated with poor outcome include age >65 years, sepsis syndrome, ANC <100 neutrophils/uL, anticipated prolonged (>10 days) neutropenia, pneumonia or other clinically documented infection, invasive fungal infections, hospitalization at the time of fever, and prior episodes of FN. If risk factors are present, therapeutic G-CSF should be considered.[10]

USE OF MGFs IN HSC TRANSPLANTATION

The term Bone marrow transplantation is now replaced with hematopoietic stem cell transplantation with introduction of peripheral blood and umbilical cord as sources of stem cell.

HSCT procedure usually carried out mainly for two reasons, to replace an abnormal hematopoietic system or to treat malignancy which is resistant to standard doses of chemotherapy, by allowing the administration of higher dose of myelo-suppressive therapy.[10]

MGFs have found to mobilize the stem cells from bone marrow to peripheral blood. For HSCT, we need early stem cells which are not yet committed to any specific cell lineage. These early stem cell have CD34 as a surface antigen, which is lost as they gets committed to specific cell lineage. Hence CD34 is used as biomarker for PBSC collection. The target concentration of PBSC for successful transplantation is around 5×10^6 CD34 cells/kg.[10]

Filgrastim is preferred compared to sargramostim. It is given as 5ug/kg for 4 days and on 5th day leukapheresis is done. Multiple sessions can be required depending upon the yield of stem cells till target of 5×10^6 is reached.

After the transplantation, it takes at least 2 to 4 weeks till these stem cells incorporate themselves into recipient bone marrow and start producing blood cells. So Filgrastim is given for 2 to 4 weeks after HSCT to correct neutropenia.[10]

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