Hematopoietic Growth Factors

Overview of Hematopoietic Growth Factors
The cellular component of blood can be divided into 3 major cell groups: RBCs (erythrocytes), megakaryocytes (which give origin to platelets), and WBCs (or leukocytes). All of these cells have their origin in a common "stem cell." This common stem cell is referred to as a pluripotent or totipotent stem cell because of its ability to differentiate down any of a number of pathways that ultimately give rise to the mature blood cell. For many years, the mechanism by which the pluripotent stem cell committed itself to a particular pathway was unknown. Although our understanding of the exact mechanisms by which this differentiation occurs is by no means complete, the discovery of growth factors has been a major advance in this area.

It is now known that a number of cytokines play a role in the differentiation of blood cells. Many cytokines that influence the development of the various hematologic cells have been identified. In all likelihood, it is the balance of these cytokines within the microenvironment surrounding the pluripotent stem cell and its subsequent lineage that determines the pathway of differentiation. Growth factors play a role in hematopoiesis not only by causing differentiation of stem cells toward a particular cell type, but also by inducing the proliferation of cells (i.e., increasing their numbers) and by favoring maturation of the cells (i.e., increasing their function) (Fig).1

The availability of growth factors has had an impact on patient care by:

- Making it possible to administer chemotherapy doses on schedule or at higher doses;
- Improving the recovery of cell counts after bone marrow or stem cell transplantation;
- Improving the ability to collect stem cells for transplantation;
- Improving the body's ability to fight infections;
- Alleviating anemia and reducing the need for RBC transfusions.1-4

The Table lists the growth factors that are currently approved for clinical use, along with their synonyms and indications. All of these growth factors are produced by recombinant DNA technology, and caution must be used in patients who have hypersensitivity to any cellular products used in the production of these factors, such as Escherichia coli, yeast, albumin, or mammalian-derived cell products.

ABSTRACT
The identification of growth factors that stimulate the proliferation and maturation of hematologic cells has been a major advance in the fields of hematology and oncology. Production of these growth factors for clinical use has had a significant impact in these and other fields by reducing the morbidity and mortality associated with diseases and treatments. Availability of these growth factors has also expanded the treatment options for many patients, particularly those with malignant neoplasms. Furthermore, the use of hematopoietic growth factors has resulted in improved quality of life for many patients.

This is the second article in a 3-part continuing education series on hematology. On completion of this article, readers will be able to list the hematopoietic growth factors available for clinical use, identify the therapeutic effect of each growth factor, enumerate the side effects of growth factors, and list the clinical indications for each growth factor.

Granulocyte Colony-Stimulating Factor (G-CSF)
G-CSF acts primarily on the neutrophil component of the blood. Its action occurs by a variety of mechanisms, including stimulation of granulocyte colonies, differentiation of progenitor cells toward neutrophil lineage, and stimulation of neutrophil maturation. Overall, it increases the number of neutrophils capable of fighting bacteria.5
G-CSF is available in various formulations throughout the world. In the United States, it is available as filgrastim. G-CSF can be administered subcutaneously or intravenously. Depending on the specific use, the dose ranges from 5 to 10 µg/kg per day. It should not be administered 24 hours prior to or 24 hours after chemotherapy. G-CSF is usually continued until the absolute neutrophil count has been greater than 500 cells/mm³ (500,000 cells/mL) for at least 3 days. G-CSF is clinically indicated for use in:

- Chemotherapy-induced neutropenia
- Collection of stem cells for transplantation
- Bone marrow or peripheral stem cell transplantation
- Congenital neutropenia

The major side effect of G-CSF is bone pain (due to the expansion of the cell population within the marrow). Transient minor side effects that have been reported with relative frequency include fever, hyperuricemia, and skin rash. Rarely, severe reactions such as anaphylaxis, capillary leak syndrome, and diffuse alveolar hemorrhage have been reported, although a causal relationship between these reactions and filgrastim administration is yet to be determined.2-5

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

GM-CSF exerts its effect via stimulation of colonies containing neutrophils, eosinophils, and monocytes (Fig 1). In the clinical setting, the effects of GM-CSF include increasing the number of neutrophils, eosinophils, and monocytes and improving the function of mature neutrophils, eosinophils, and monocytes.

GM-CSF is available as sargramostim in the United States. The dose of GM-CSF varies from 250 to 500 µg/m², depending on the specific use.5 It is approved for use in:

<table>
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<tr>
<th>Growth Factor</th>
<th>Synonyms</th>
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<tr>
<td>Granulocyte colony-stimulating factor</td>
<td>G-CSF, rG-CSF, rhG-CSF, filgrastim</td>
<td>Chemotherapy-induced neutropenia; stem cell collection for transplantation; bone marrow and/or peripheral stem cell transplant; congenital neutropenia, idiopathic neutropenia, cyclic neutropenia</td>
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<tr>
<td>Granulocyte-macrophage colony-stimulating factor</td>
<td>GM-CSF, sargramostim, rGM-CSF, rhGM-CSF</td>
<td>Chemotherapy-induced neutropenia; stem cell collection for transplantation; bone marrow and/or peripheral stem cell transplant</td>
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<td>Erythropoietin</td>
<td>Epoetin alpha, epoetin beta</td>
<td>Anemia associated with chronic renal failure, chemotherapy, AIDS, prematurity, rheumatoid arthritis, and prior to elective surgery to reduce need for allogeneic blood transfusions</td>
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<tr>
<td>Oprelvekin interleukin-11</td>
<td>rhlL-11, rIL-11, recombinant human interleukin-1</td>
<td>Prevention of chemotherapy-induced severe thrombocytopenia</td>
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</table>

CSF indicates colony-stimulating factor; G, granulocyte; GM, granulocyte-macrophage; IL, interleukin.
■ Chemotherapy-induced neutropenia
■ Bone marrow or peripheral stem cell transplantation
■ Collection of stem cells for transplantation

GM-CSF has many side effects similar to G-CSF, although the frequency of these may be higher due to its effect on inflammatory cytokines. These side effects include skin rash, diarrhea, fever, malaise, chills, and headaches.1,2,3

**Erythropoietin**

Erythropoietin stimulates stem cells toward the production of RBCs. Its clinical result is usually not seen before 7 days after initiating therapy and may take as long as 14 days. It can be administered intravenously, intramuscularly, or subcutaneously. Prior to initiating therapy, one should ascertain that the patient has adequate iron stores to sustain the increased hemoglobin production. Erythropoietin is indicated for treating patients with anemia from a variety of causes, including:

■ Chronic renal failure (with or without dialysis)
■ AIDS
■ Chemotherapy
■ Neonatal anemia due to prematurity
■ Rheumatoid arthritis

It is also indicated to prevent or reduce the need for allogeneic blood transfusions in surgical patients.

The dose of erythropoietin ranges from 50-150 U/kg 3 times weekly for most patients, although in chemotherapy patients and those undergoing elective surgery, the dose can be increased to as high as 300 U/kg. Studies have demonstrated that erythropoietin can be effective at 40,000 U once a week. This dose schedule has received approval from the Food and Drug Administration. Once the hematocrit has reached the 30% to 36% (0.30-0.36) range, the erythropoietin should be reduced to a maintenance dose.

The side effects of erythropoietin are minimal with the predominantly reported adverse events being bone pain, headaches, hypertension, and, rarely, thrombocytosis with venous fistula occlusion.2,4

**Oprelvekin**

Oprelvekin is recombinant human interleukin-11. It stimulates megakaryocytic progenitor stem cells and maturation of megakaryocytes with the eventual result of increasing platelet production. Oprelvekin is indicated for the prevention of severe thrombocytopenia and to reduce the need for platelet transfusions after standard chemotherapy. It is not indicated for use in high-dose chemotherapy (ie, bone marrow transplantation). It is administered subcutaneously daily at 50 µg/kg starting 6 to 24 hours after chemotherapy and for up to 21 days after chemotherapy. It should be discontinued at least 2 days before chemotherapy.

The major disadvantage with oprelvekin has been the relatively high incidence of side effects in the study populations. The most serious of these include cardiac arrhythmias, headache, nausea, edema, and dyspnea. Most of these are considered to be due to an increase in plasma volume associated with oprelvekin. Antibodies against oprelvekin have been reported, although the clinical consequence of their presence (eg, do they reduce the therapeutic benefit?) is not yet known.

**Future Applications**

The use for these growth factors, as well as others under investigation, is certain to expand. As the knowledge about the effects that these growth factors exert on various cell lines and cytokine production increases, so will the applications for these substances. Some areas of ongoing research activity include ex vivo expansion of stem cell products from a variety of sources (bone marrow, peripheral blood, liver), gene therapy, and altering the cytokine response to immunologic events (eg, infections, organ rejection).

**Conclusion**

Currently available hematopoietic growth factors can improve the production of 3 major blood cell groups. The availability of these growth factors has had a major impact the treatment of a variety of illnesses, both malignant and nonmalignant. As with any other therapy, the use of these growth factors must be assessed with regards to their proven clinical efficacy, side effect profile, and cost-containment measures.1

**References**