Hematopoiesis, Growth Factors and Immunology

Melinda Chouinard, RN, BSN, OCN
Clinical Services Manager
MultiCare Regional Cancer Center

Outline

• Formation of blood cells (hematopoeisis)
  – Cells of the Myeloid line
  – Cells of the Lymphoid line
• Growth Factors
• Role of the immune system
• New directions of cancer therapy

Objectives

• Describe the hematopoietic system.
• Identify differences between innate and acquired immunity
• Review areas of research for innovative therapies

Why do we need to know this?

• Understand side effects that occur because of disruptions in the production of blood cells
• Understand side effects that occur because of disruptions in the immune system
• Understand treatments aimed at utilizing body’s own mechanisms to fight cancer and mitigate side effects
The Nurse’s Role

• What is the patient at risk for?
• What are the primary nursing interventions?
• What education should be provided?
• What is on the horizon?

What is this and what does it do?

What about this?

What are these?
These cells and others all have two things in common:
1. They originate from a common progenitor cell
2. They get to where they are through a process called hematopoiesis

Hematopoiesis

- Process of blood cell formation
  - Red blood cells
  - Platelets
  - White blood cells
  - Other cells

- Greek origin
  - “Haima”: blood
  - “Poiesis”: to make

Bone Marrow Environment

- Vessels
- Marrow Sinuses
- Marrow Stroma
  - Supportive structure
  - Regulatory proteins
- Cells

Bone Marrow

4 Year Old   80 Year Old
Pluripotent Stem Cell

- Hematopoietic cell
- Source of all cells
  - "uncommitted"
  - Progenitor
- Self renewing
- Location
  - Marrow
  - Peripheral Blood (CD34+)
- Migratory properties

Identifying Hematopoietic Stem Cells

- **CD 34** Cell
  - Cluster of differentiation antigen
  - Cell surface marker
  - Utilized to identify stem cells
  - Dendritic cells used in novel therapies are cultured from the CD34+ cells
  - Non-specific
    - Expressed on leukemic cells
    - 30% of CD34+ collected cells are not progenitors

Hematopoiesis

- Proliferation
- Differentiation

Commitment

- **Myeloid Lineage**
  - Erythrocyte
  - Platelet
  - Granulocyte
    - Neutrophil
    - Basophil/mast cell
    - Eosinophil
  - Monocyte / macrophage
  - Dendritic cell – Antigen Presenting Cell

- **Lymphoid Lineage**
  - B lymphocyte
  - T lymphocyte
  - Dendritic Cell – Follicular Presenting Cell

- Natural Killer Cell (NK)
Differentiation

Erythrocytes

- **O₂/CO₂ transport and exchange**
- **Acid Base Balance**
- **Production 2.5 billion/kg/day**
- **Life span of 108 - 120 days**
- **60 – 90 days for pts on chemo!**
- **Hgb: O₂ carrying protein, written as gm/dl**
  - M: 14-18 gm/dl
  - F: 12-16 gm/dl
- **Hct: %age of RBC in 100 ml of blood**
  - M: 42-54%
  - F: 32-46%

Be aware of institutional & lab differences in the ranges

Anemia

- **Caused by**
  - Decreased production of RBC
  - ↓ epoetin production
  - Increased destruction of RBC
  - Blood loss

- **Risk Factors**
  - Cancer
  - Radiation
  - Myelosuppressive chemotherapy
  - Platinum containing regimens
  - Low Hgb prior to start of chemo

Incidence ≈ 50%

Higher incidence with subsequent treatments.
Anemia - Treatment

- Red Blood Cell transfusion
- Iron, folate and B₁₂ supplementation
- Erythropoietin stimulating agents
  - Epoetin [Procrit®, Epogen®]
  - Darbepoetin [Aranesp®]
  - Contraindicated in uncontrolled hypertension
  - Side effects: fatigue, allergic reactions, hypercoagulability of blood, diarrhea, fever

Mechanism of action

- Erythropoietin (EPO) interacts directly with the EPO receptor on the red blood cell (RBC) surface
- Activates signaling pathways, resulting in the proliferation & differentiation of erythroid precursor cells
- Provides protection from apoptosis of RBC precursors.
- Magnitude of increase in RBC concentration in response is primarily controlled by the length of time EPO concentrations are maintained

Polycythemia

- Overabundance of RBCs, often with Hct >55%
- May be result of myeloproliferative disorders, can also be related to altitude or have other causes (heredity, malignancy)
- Treatment usually therapeutic phlebotomy, may use hydroxyurea
- Symptoms include a characteristic ruddy skin tone and headaches
Thrombocytes

- Hemostasis
- Normal: 150,000 – 400,000 cells/mm³
- Production: 2.5 billion/kg/day
- Life span 7 - 10 days

Thrombocytopenia

- Decreased number of circulating platelets
- Signs/symptoms of bleeding:
  - petechiae
  - bruising
  - overt/occult:
    - oral
    - nasopharynx
    - GI
    - urinary tract

Thrombocytopenia

- Treatment
  - Platelet transfusion
  - Other treatments do not have established effectiveness.
    - Neumega (oprelvekin) may reduce requirements for platelet transfusions but the need for this should be weighed against side effects.

Thrombocythemia

- Elevated platelet count >600,000
- May have no symptoms
- May have the following:
  - Burning or throbbing pain in feet
  - TIA
  - Thrombosis
  - Enlarged spleen (~50%)
- Treatment
  - Hydroxyurea
  - Anagrelide
Leukocyte Function

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Function</th>
<th>When Absent:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil</td>
<td>Phagocytosis</td>
<td>Bacterial Infection</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>Allergic Rxn, defense parasite</td>
<td>Parasitic infections</td>
</tr>
<tr>
<td>Basophil</td>
<td>Allergic/Inflamm Rxn</td>
<td>Inadequate inflammatory response</td>
</tr>
<tr>
<td>Monocyte</td>
<td>Phagocytosis</td>
<td>Fungal infection</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>Immunity</td>
<td>Viral, opportunistic infection, cancer</td>
</tr>
</tbody>
</table>

Neutrophils – Capacity for Infection Fighting/Defense

- **Advantages**
  - limited stimuli provoke a response
  - early response in large numbers
  - effective killing bacteria, digest debris (healing)
- **Disadvantages**
  - unable to recognize many injurious agents
  - cannot modify response (i.e. doesn’t “learn”)
  - Short lifespan of 3-6 hours in blood

Neutrophils

- **Normal Values**
  - 60%-80% of total WBC count (1800-7700 cells/mm³)
  - majority stored in marrow
  - Live 9 days in marrow, up to 5 days in tissue but only 3.6 – 10 hours in bloodstream
  - Produce 1 billion/kg/day
- **Phagocytic cells**
  - Early responder to infection
  - when low: susceptible to bacterial infection
- **What types of patients might be susceptible to infections due to neutrophil counts?**
Neutrophil

- Functional Neutrophils
  - Banded neutrophil (Band) - less mature
  - Polymorphonuclear cell (polys) or segmented neutrophil

![images of Band and Polys/Seg]

Absolute Neutrophil Count (ANC)

- Represents number of functional neutrophils
  - Number of circulating Polys (segs or PMN) + Bands
- Used as an indicator to determine:
  - Risk of infection
  - Ability to continue therapy

You will talk about this more on day 2

Leukopenia

- Leukopenia – reduced number of WBC
- Consequences of leukopenia
  - Increased hospital admissions
  - Increased risk for infection
  - Higher costs of treatment
  - Delay in treatment
    - Increased risk of unsuccessful treatment
- Treatment using growth factors
  - Filgrastim, pegfilgrastim

![Hematopoiesis diagram]
The Immune System

The immune system is an integrated system that has 4 primary functions:
- Protection
- Surveillance
- Homeostasis
- Regulation

Immune system: Innate vs. Adaptive immunity

<table>
<thead>
<tr>
<th>Features</th>
<th>Innate</th>
<th>Adaptive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary defense</td>
<td>Secondary defense</td>
</tr>
<tr>
<td></td>
<td>Non-specific</td>
<td>Specific</td>
</tr>
<tr>
<td></td>
<td>No memory</td>
<td>Has memory</td>
</tr>
<tr>
<td>Inflammatory response:</td>
<td>Phagocytic cells respond to bacteria, fungus and parasites</td>
<td>Lymphocytes respond:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T cells—surveillance, rejection, virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B cells—antibody, virus, bacteria</td>
</tr>
<tr>
<td>Components</td>
<td>Skin and mucous membranes</td>
<td>Lymphoid system</td>
</tr>
<tr>
<td></td>
<td>Phagocytic cells</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td></td>
<td>Complement system</td>
<td>antibodies</td>
</tr>
</tbody>
</table>
Structures of the immune system

• Skin & Mucous Membranes
  – Mechanical barrier
    • Intact
    • Shedding epidermis and mucosal cells
  – Chemical barrier
    • pH of skin
    • Secretions of antimicrobial chemicals (in saliva, mucus, tears and sweat)
• Lymphoid system

- Natural Killer cells (CD56+)
  – Lymphocytes
  – Lack markers found on B and T cells
  – Kill tumor cells and virally infected cells without previous exposure
  – Non-specific: can respond to a variety of antigens
  – Part of the innate immune system
• Antigen presenting cells:
  – Macrophages
  – B cells
  – Dendritic cells ...these cells can initiate a primary immune response

Immune System: Monocytes

• Monocytes patrol the bloodstream
• "sample" surroundings
• present antigen of ingested material
• secrete cytokines
• if absent: ↑ fungal infections

Immune system: Macrophage

• Precursor: Monocyte
• Greek: big eaters, from makros "large" + phagein "eat"
• Found in tissue
• Versatile
• Present antigens
• Scavenge
Dendritic Cell

- Antigen Presenting Cell (APC)
  - Recognized as major cells in the immune system 1973
  - Phagocytic cells
  - Present antigen of ingested material
  - Single cell can activate 100-3,000 T cells

Adaptive Immunity

- Humoral immunity: utilizes B lymphocytes, memory B cells and plasma cells. End result is the production of immunoglobulins
- Cell-mediated immunity: Mediated by T-cells and cytokines. No antibodies involved but uses cytotoxic T cells (CD 8+) and Helper T cells (CD4+)

FROM: Polovich: Chemotherapy and Biotherapy Guidelines, pp 27-30
Lymphocytes

- Specific/Adaptive immunity
- Differentiate between self and non-self (self tolerance)
- T Lymphocytes
  - Cell mediated immunity
- B Lymphocytes
  - Humoral immunity
- Natural Killer cells (NK)

- 20% of total WBC count
- If absent: ↑ viral infections

B (Bone Marrow) Lymphocytes

- Humoral/Specific Immunity
  - Plasma cell precursors
  - These respond to antigens and produce immunoglobulins.
  - Immunoglobulins (aka antibodies) are protein products of the plasma cells, there are 5 major Ig’s

T (Thymus) Lymphocyte

- Cellular/Specific Immunity
  - Cytotoxic T cells (CD8+) kill foreign cells and cells that have viral infections
  - T-Helper cells (CD4+) stimulate B cells, call in phagocytes and activate other T cells…immune response coordinators
  - T-regulatory cells/suppressor T – interfere with the immune response, work to help prevent development of autoimmunity
  - Memory T cells recognize specific antigens

Immune system - Role in cancer prevention/control

- Detect and destroy cancer cells through recognition of non-self
  - Cancer cells have non-self antigens on surface – tumor associated antigens
- Theory of how malignant cells elude immune system
  - internalize cell-surface Ag
  - glycoproteins cover-up antigenic markers
  - tumor cells closely resemble normal cells
Fast facts

- Immunosuppression associated with increased risk of malignancy
- Patients who had a strong immune response that infiltrated some specific types of tumors with T cells or NK cells have a more favorable prognosis

Using the Immune System to treat Cancer

- Monoclonal antibodies – used to bind to specific antigen on a cell surface
- Therapeutic vaccines: dendritic cells studies as a means to induce immunity...
  - “Personalized” vaccine using specific genetic profile of the tumor
  - Disease-specific vaccine

Novel Therapies

- Provenge—metastatic prostate cancer
- GBM –novel vaccine under study
- Malignant Melanoma: ipilimumab and tremelimumab block a specific molecule and allows increased immune system activity against tumor antigens.
- CLL: Novel investigational agent
Vaccines

- Use dendritic cells (or antigen presenting cells [APC])
- Culture dendritic cells
  - CD34+ bone marrow precursor cells
  - CD14+ monocytes
- Load with tumor lysates or antigens from the patient
- Re-infused
- Provoke immune response against tumor

Using the Immune System to treat Cancer

- Prophylactic vaccines
- Cytokines
  - Interferon \(\alpha\)
  - Interleukin
  - Colony stimulating factors

The immune system may be able to recognize and destroy cancer cells due to the presence of:

a. Endotoxins
b. embryonic oncogenes
c. tumor associated antigens
d. anaplastic antibodies

Resources

- National Comprehensive Cancer Network [www.nccn.org]