Objectives

- Describe signs and symptoms of cytokine release syndrome and neurotoxicity
- Describe nursing management of these toxicities

Effector Cell Therapy

- Immune effector cell therapies are capable of modulating or effecting a specific immune response.
- T-cells bind to a target antigen on a tumor cell and cause activation of the receptor which promotes T cell proliferation and killing of the tumor cell
- During this process, a large variety of cytokines may be released from the T cells and from accessory cells.

What Are Cytokines?

- Small proteins
- Produced and secreted by a range of cells including immune cells
- Act as chemical messengers
- Influence the behavior of cells around them

Function Of Cytokines

- Mediate normal cellular processes
  - Production of blood cells
  - Promotion or inhibition of cell growth and differentiation
- Help regulate the immune response
  - Coordinate communication between the immune system and organs
  - Activate lymphocytes and other immune effector cells
  - Regulate the inflammatory response
Role Of Cytokines In Immune Response

Cytokine Release Syndrome (CRS)
- General inflammatory condition
- Occurs when lymphocytes and/or myeloid cells become highly activated and release excessive inflammatory cytokines

Immune System Imbalance
- High levels of immune activation required for clinical benefit
- Immune therapies are becoming more potent
- Magnitude of immune activation exceeds the physiologic norm

Characteristics Of CRS
- Clinically manifests as a constellation of symptoms
- Frequency, rate of onset and level of toxicity vary amongst different effector cell therapies
- Incidence and severity greater in patients with large tumor burdens
- IL-6 has been implicated as a central mediator of toxicity in CRS
- C-Reactive Protein can be used as a biomarker

Clinical Manifestations Of CRS
- Constitutional Symptoms
  - Fever - the hallmark symptom
  - Chills/Rigors
  - Myalgia/Arthralgias
  - Skin rash
- Gastrointestinal
  - Nausea/Anorexia
  - Diarrhea
- Cardiac dysfunction
  - Tachycardia
  - Hypotension
  - Diminished cardiac output
  - Arrhythmias
- Respiratory distress
  - Tachypnea
  - Dyspnea
  - Hypoxemia
- Renal and Hepatic dysfunction
  - Acute kidney injury
  - Transaminitis
  - Hyperbilirubinemia
Clinical Manifestations Of CRS

- Coagulopathy
  - Elevated D-dimer
  - Low fibrinogen
  - Disseminated intravascular coagulation
- Neurologic
  - Headache
  - Aphasia
  - Seizures
  - Coma

CRS Management

- Balancing act
- Goal of management
  - Control symptoms
  - Prevent life threatening toxicity
  - Maximize the potential for antitumor effects
  - Management directed by the grade of toxicity
- Different products have different management guidelines

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description of Symptoms</th>
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<tbody>
<tr>
<td>1: Mild</td>
<td>Not life-threatening, require only symptomatic treatment such as antipyretics and antiemetics (e.g., fever, chills, fatigue, headache, malaise)</td>
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| 2: Moderate | Require and respond to moderate intervention:  
  - Oxygen requirement ≤ 40%, or  
  - Hypotension responsive to fluids or low-dose of a single vasopressor, or  
  - Grade 2 organ toxicity (by CTCAE v4.03) |
| 3: Severe | Require and respond to aggressive intervention:  
  - Oxygen requirement ≥ 40%, or  
  - Hypotension requiring high-dose of a single vasopressor (e.g., norepinephrine ≥ 20 µg/min, dopamine ≥ 20 µg/kg/min, phenylephrine ≥ 200 µg/min, or ephedrine ≥ 10 µg/min), or  
  - Hypotension requiring multiple vasopressors (e.g., vasopressin + one of the above agents, or combination vasopressors equivalent to ≥ 20 µg/min norepinephrine), or  
  - Grade 3 organ toxicity or Grade 4 transaminitis (by CTCAE v4.03) |
| 4: Life-threatening | Life-threatening:  
  - Requirement for ventilator support, or  
  - Grade 4 organ toxicity (excluding transaminis) |
| 5: Fatal | Death |

Commercial Product Guidelines

- Urgent consult with IMTX Attending or study PI
- Pharmacy to maintain adequate “par” of Tocilizumab on site
- Tocilizumab must be ordered within designated PowerPlan

SCCA/UW Policy
ORCA Ordering Of Tocilizumab

Nursing Interventions For Mild to Moderate CRS
- Manage fever
  - Infection assessment with cultures
  - Antipyretic
  - Initiate empiric antibiotic therapy
- Monitor for organ dysfunction
  - Assess vitals at least every 4 hours
  - Follow daily CBC, electrolytes, hepatic function, LDH, coagulations factors, ferritin, C reactive protein, and IL 6 levels
- Neurologic assessments
- Symptomatic support
  - Antiemetics
  - Supplemental oxygen
  - Fluid bolus and low dose vasopressors
  - Seizure prophylaxis

Nursing Interventions For Severe To Life Threatening CRS
- Aggressive intervention
  - Tocilizumab or other cytokine directed infusion
  - Dexamethasone administration
  - Blood product administration
  - Multiple or high dose Vasopressors
  - Dialysis
  - ICU care
  - Ventilator support

Case Presentation
- 69 yo male with CLL diagnosed in 2011
- History of interest: TIA or migraines x 3 on Plavix since 2014
- Pre effector therapy staging showed PB flow with 24.7% abnormal B cells and a BM flow with a 72.3% abnormal B cell populations.
- Lymphodepletion with Cytoxan and Fludarabine 5/10-5/12
- CD19 directed CAR T cells on 5/15

Neurotoxicity
- Presentation and pathogenesis not completely understood
  - Elevated IL-6 levels
    - Disturbance of the endothelial tissue
    - Blood-brain barrier disruption
- Risk factors
  - High tumor burden in marrow
  - High fever
  - Incidence about 40%
- May occur at the same time as CRS or may arise as other symptoms are resolving.
- Most neurologic adverse events are reversible.

Manifestations Of Neurotoxicity
- Headache
- Drowsiness
- Agitation/ irritability
- Confusion, delirium
- Word finding difficulty
- Frank aphasia
- Mental status changes
- Hallucinations
- Tremors
- Altered gait
- Seizures
- Coma
Interventions For Neurotoxicity

- Prophylactic Keppra
- Mini mental status exams
- Neurology consult
- Lumbar puncture
- MRI of brain
- Steroids
- Supportive care with focus on patient safety

Toxicity Management Guidelines

Summary

- Modern immunotherapies show impressive promise
- Unique set of toxicities
- Nurses are in the forefront of assessment, identification and management of these toxicities
- Management is critical
- Interventions are therapy specific

Reference And Resources

- Cytokine release Syndrome: Overview and nursing implications, Sheila Breslin, CJON Vol 11, Number 1
- Cytokine Release Syndrome: IP care for side effects of CAR T cell therapy, Laura Smith, CJON, Vol 21, Number 2
- Current concepts in the diagnosis and management of cytokine release syndrome, Daniel Lee, Blood Vol 124, number 2
- Cytokine release syndrome (CRS) and neurotoxicity (NT) after CD19-specific chimeric antigen receptor-(CAR-) modified T cells., Cameron Turtle, JCI, 2017 supp 3020

Thank you