What are cytokines?

- Polypeptide proteins
- Produced and secreted by most cells in the human body
- Families of cytokines
  - Interleukins
  - Interferons
  - Tumor necrosis factor
  - Colony-stimulating factors

Function of Cytokines

- Act as chemical messengers
- Facilitate communication among cells
- Coordinate responses among the immune system and organs
  - Activation of lymphocytes and other immune effector cells
  - Mediation of inflammatory response

Immune Activation in Cancer treatment

- Immune system recognizes something, like a cancer cell, as foreign
- Immune effector cells, like T cells, target the foreign substance
- The engagement of the T cell to the foreign substance further activates the immune system
- The cancer cell is targeted for destruction
- When the cell is destroyed cytokines are released

Cytokine Release Syndrome (CRS)

- General inflammatory condition
- Manifests when lymphocytes and/or myeloid cells become activated and release inflammatory cytokines
- Clinically manifests as a constellation of symptoms
- Potentially life threatening toxicity of immune therapy
Clinical Manifestations of CRS

- Constitutional Symptoms
  - Fever - the hallmark symptom
  - Chills
  - Myalgia
  - Nausea
- Cardiac dysfunction
  - Tachycardia
  - Hypotension
  - Diminished cardiac output

Clinical Manifestations of CRS

- Respiratory distress
  - Tachypnea
  - Dyspnea
  - Hypoxemia
- Renal and Hepatic dysfunction
  - Capillary leak syndrome
  - Transaminitis
  - Hyperbilirubinemia

Coagulopathy

- Elevated D-dimer
- Disseminated intravascular coagulation

Neurologic

- Headache
- Aphasia
- Seizures
- Coma

Grading Criteria for CRS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description of Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Rare</td>
<td>Not life-threatening, require only symptomatic treatment such as antipyretics and anti-emetics (e.g., fever, nausea, fatigue, headache, myalgia, malaise)</td>
</tr>
<tr>
<td>1: Moderate</td>
<td>Require and respond to moderate intervention: oxygen requirement &lt; 40%, or hypotension responsive to fluids or low dose of a single vasopressor, or Grade 2 organ toxicity (by CTCAE v4.03)</td>
</tr>
<tr>
<td>2: Severe</td>
<td>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 ≥ 10 µg/kg/min, phenylephrine ≥ 100 µg/min, or epinephrine ≥ 5 µg/min), or hypotension requiring multiple vasopressors (e.g., vasopressin + one of the above agents, or combination vasopressor equivalent to ≥ 20 µg/min norepinephrine), or Grade 3 organ toxicity or Grade 4 transaminitis (by CTCAE v4.03)</td>
</tr>
<tr>
<td>3: Life-threatening</td>
<td>Life-threatening: requirement for ventilator support, or Grade 4 organ toxicity (excluding transaminitis)</td>
</tr>
<tr>
<td>4: Fatal</td>
<td>Death</td>
</tr>
</tbody>
</table>

Risk Assessment for CRS

- Incidence and severity appear greater in patients with large tumor burdens
- Symptom onset typically occurs days to weeks after the immune therapy
- Timing coincides with maximal in vivo T cell expansion
- IL-6 has been implicated as a central mediator of toxicity in CRS
- C-Reactive Protein can be used as a biomarker

CRS management

- Balancing act
- Goal to treatment
  - control symptoms
  - prevent life threatening toxicity
  - maximize the potential for antitumor effects
Treatment algorithm

Nursing Interventions For CRS

• Patient and laboratory monitoring
  • Infection assessment
  • Vitals at least every 4 hours
  • Cardiac monitoring
  • Neurologic assessments
  • Daily CBC, electrolytes, hepatic function, LDH, coagulation factors, ferritin, C reactive protein, and IL 6 levels
  • Organ function assessment

• Supportive care
  • Infection prophylactic treatment
  • Antipyretic
  • Antiemetics
  • Supplemental oxygen
  • Fluid bolus

Nursing Interventions For CRS

• Aggressive care
  • Blood product administration
  • ICU care
  • Vasopressors
  • Dialysis
  • Dexamethasone administration
  • Tocilizumab infusion

Neurotoxicity

• May occur at the same time as CRS or may arise as other symptoms are resolving.
• Presentation and pathogenesis not completely understood
  • Elevated IL-6 levels
  • Disturbance of the endothelial tissue
  • Blood-brain barrier disruption
• Risk factors
  • Higher burden of malignant B cells in marrow
  • Higher infused CAR-T cell dose
  • Higher fever
• Most neurologic adverse events are reversible.

Manifestations Of Neurotoxicity

• Headache
• Confusion, delirium
• Word finding difficulty or frank aphasia
• Mental status changes
• Hallucinations
• Tremor
• Altered gait
• Seizures
• Coma
**Interventions For Neurotoxicity**

- Baseline studies to evaluate neurologic status
  - Mini mental status exams
  - Lumbar puncture
  - MRI of brain
- Prophylactic Keppra
- Ongoing assessment of neurologic status
- Reorientation
- Supportive care with focus on patient safety

**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