CYTOKINE RELEASE SYNDROME

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How the Experts Treat Hematologic Malignancies
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DISCLOSURES

No Disclosures
Objectives

• Review cytokine release syndrome
• Discuss diagnostic capabilities and limitations
• Review clinical presentation and grading of cytokine release syndrome
• Discuss management of severe cytokine release syndrome
Immune Surveillance in Cancer
Cancer Immunotherapy

- Better understanding of immune surveillance and tumor growth have led to therapeutic advances in oncology
- Immune-based therapies are becoming more prevalent in the treatment of cancer
- Unique toxicities associated with immune-based therapies
- Important to be able to recognize these toxicities and know how to manage them
Cytokine Release Syndrome

- Constellation of inflammatory symptoms resulting from elevated levels of cytokines including IL-6, IFN and TNF-α
- Treatment antibodies bind to T-cell receptors → T-cells activated → cytokines released
- Most common adverse event associated with novel immunotherapies (blinatumomab, CART-19)
Incidence and Severity

- Symptoms can range from mild and flu-like to severe multi-organ system failure and death
- Onset and severity of symptoms depend on type of agent and level of immune cell activation
- Contributing Factors:
  - Disease type
  - Tumor burden
  - T-cell dose
Therapies Associated with CRS

- Monoclonal antibodies
  - Rituxan
- Bispecific T-cell engagers
  - Blinatumomab
- Adoptive immunotherapies
  - Chimeric antigen receptors (CAR) T-cells
Diagnosis and Grading
Biomarkers

• Circulating cytokine levels could potentially serve as biomarkers to diagnose and quantify severity of CRS

• Limitations:
  – Requires CLIA certified assays, which are not readily available in most hospitals
  – Correlation between inflammatory cytokine levels and severity of CRS still unclear
Ferritin

- Reported correlation between significantly elevated ferritin levels and CRS
- Limitation: definitive level not yet established
IL-6

- Rising level of IL-6 is a strong predictor of CRS
- Changes in IL-6 level precede elevation of CRP
- Limitations:
  - Real time measurement of IL-6 is not readily available in most hospitals
C-Reactive Protein

- Acute phase reactant that is synthesized by the liver in response to elevated IL-6
- CRP assay is rapid, inexpensive, available in most hospitals
- CRP level of ≥ 200mg/L is linked to CRS with good sensitivity and specificity
- Limitations: can also be elevated during infection
## Clinical Presentation

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Fevers (hallmark) ± rigors, malaise, fatigue, anorexia, myalgias, arthralgias</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea, hypoxemia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, hypotension, widened pulse pressure, increased cardiac output (early), diminished cardiac output (late)</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Elevated D-dimer, hypofibrinoginemia ± bleeding</td>
</tr>
<tr>
<td>Renal</td>
<td>Azotemia</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Transaminitis, hyperbilirubinemia</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache, mental status changes, confusion, delirium, aphasia, hallucinations, tremor, altered gait and coordination, seizures</td>
</tr>
</tbody>
</table>
## Grading Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Toxicity</th>
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| Grade 1 | Symptoms are not life threatening and require symptomatic treatment  
- Fever, nausea, fatigue, headache, myalgias, malaise |
| Grade 2 | Symptoms require and respond to moderate interventions  
- Oxygen requirement < 40%  
- Hypotension responsive to fluids or single, low dose vasopressor  
- Grade 2 organ toxicity |
| Grade 3 | Symptoms require and respond to aggressive intervention  
- Oxygen requirement ≥ 40%  
- Hypotension requires high dose or multiple vasopressors  
- Grade 3 organ toxicity or grade 4 transaminitis |
| Grade 4 | Life-threatening symptoms  
- Requirement for ventilator support  
- Grade 4 organ toxicity |
| Grade 5 | Death |
Treatment Algorithm
**CRS Grading Assessment**

**Treatment**

**Grade 1 CRS**
- Fever (≥ 38.3)
- Constitutional symptoms

**Grade 2 CRS**
- Hypotension: responds to fluids or one low dose vasopressor
- Hypoxia: responds to < 40% O2
- Organ toxicity: grade 2

**Grade 3 CRS**
- Hypotension: requires multiple or high dose vasopressors
- Hypoxia: requires ≥ 40% O2
- Organ toxicity: grade 3, grade 4 transaminitis

**Grade 4 CRS**
- Mechanical ventilation
- Organ toxicity: grade 4, excluding transaminitis

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**Extensive comorbidities or older age?**

- **No**
  - Vigilant supportive care
  - Assess for infection (treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics)

- **Yes**
  - Vigilant supportive care
  - Monitor cardiac and other organ function closely

- **Yes**
  - Tocilizumab
  - +/- corticosteroids
Management

- Work-up to exclude infection or other cause
- Fluid resuscitation and vasopressors
- Antipyretics
- Broad spectrum antibiotics
- Supplemental oxygen
- Tocilizumab +/- corticosteroids
Tocilizumab

• Humanized monoclonal antibody against IL-6 receptors
• IL-6 blockade with tocilizumab demonstrated rapid reversal of life-threatening symptoms
• First choice therapy for CRS
• Dosing:
  – 4-8 mg/kg
  – Infused over 1 hour
  – Repeat in 24-48h if no clinical improvement
Tocilizumab: Side Effects

• Side effects:
  – transaminitis, hypercholesterolemia, thrombocytopenia,
  – neutropenia (uncommon, resolved with discontinuation of agent)

• Black box warning: increased incidence of infection (viral, bacterial, fungal, mycobacterial)

• No acute infusional toxicities observed
Tocilizumab: Response

• Resolution of fevers and hypotension within a few hours

• If no improvement or stabilization occurs within 24 hours, repeat dose +/- additional immunosuppressive agent (corticosteroids)

• Lack of response:
  – ? ongoing production of IL-6
  – ? inadequate dosing
  – ? unknown factors
Corticosteroids

- Corticosteroids also effective in treatment of CRS
- Second line therapy
- Preferred for severe neurotoxicity
- Potential adverse effects on antitumor activity of adoptively transferred T-cells

- Type and dosing:
  - Methylprednisolone 2 mg/kg/day
  - Dexamethasone 0.5 mg/kg, maximum 10 mg/dose
